MULTIFACETED INSIGHTS INTO CLUSTER HEADACHE FUNCTIONAL NEUROIMAGING, SACCADOMETRY AND QUALITY OF LIFE

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MULTIFACETED INSIGHTS INTO CLUSTER HEADACHE: FUNCTIONAL NEUROIMAGING, SACCADOMETRY AND QUALITY OF LIFE

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To my loving husband, Ruddin

and my bundles of joy, Syakir and Waliy

ABSTRACT

Cluster headache (CH) is a highly disabling primary headache disorder, characterized by strictly unilateral, excruciating pain in the distribution of the trigeminal nerve with associated cranial autonomic symptoms, that has a significant impact on patients' health-related quality of life (HRQoL). There has been great interest over the years in elucidating the pathogenesis of this disorder.

This thesis adopted a mixed methods approach, using saccadometry and functional magnetic resonance imaging (fMRI) studies to gain better insight to the underlying processes involved, whilst also studying the disability and resultant impact it has on patients' HRQoL. Arterial spin labeling (ASL) was utilized to identify changes in regional cerebral blood flow (rCBF) relating to brain responses to a greater occipital nerve block (GONB), which is a widely used transitional treatment. Significant activations were observed during the interictal period in several brain regions known to be involved in pain processing, including the posterior hypothalamus, a structure that has been hypothesized to have a crucial role in CH. This implies that a central permissive state exists during a bout, with subsequent deactivations following the GONB. A study of visual saccadic latencies revealed that CH patients have longer mean latencies with high variability and reduced number of fast saccades. This suggests that there is a delay in decision-making in CH patients, possibly stemming from basal ganglia dysfunction, with high variability of latencies arising from probable dysfunction within the noradrenergic system. This corresponds with the fMRI findings, therefore suggesting a pivotal role of these systems in CH pathophysiology.

Due to the lack of a specific HRQoL measure for CH, a 28-item CH specific HRQoL (CHQ) scale was developed and validated, showing good internal consistency,

validity and test-retest reliability. An assessment made of the HRQoL confirmed the significant impact it has on patients' lives, especially for those with the chronic variant.

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PUBLICATIONS

Abu Bakar N, Chard D, Matharu MS. Bilateral paroxysmal cephalalgia: a novel indomethacin-responsive primary headache syndrome? Cephalalgia. 2012;32(13):1005-8.

Lambru G, Abu Bakar N, Stahlhut L, McCulloch S, Miller S, Shanahan P, et al. Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. European Journal of Neurology. 2013.

Lambru G, Bakar NA, Matharu M. SUNA and red ear syndrome: a new association and pathophysiological considerations. J Headache Pain. 2013;14(1):32.

Abu Bakar N and Renton T. Trigeminal autonomic cephalalgias- TACs: a review of neuroimaging studies. Journal of the Lebanese Dental Association. 2013; 48 (2): 14-19.

Abu Bakar N and Matharu M. Trigeminal Autonomic Cephalalgias. Dental Update. 2014 (in press) and book chapter (Stephen Hancocks Limited) 2014 (in press).

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ADL	Activities of daily living
AS	Acceptance of Illness
ASL	Arterial spin labeling
BET	Brain extraction tool
BOLD	Blood oxygen level dependent
BP	Bodily pain
CASL	Continuous arterial spin labeling
CCH	Chronic cluster headache
CCSI-R	The Cognitive Coping Strategies Inventory – Revised
CDH	Chronic daily headache
CH	Cluster headache
CHQ	Cluster headache specific quality of life
CTTH	Chronic tension-type headache
DBS	Deep brain stimulation
ECH	Episodic cluster headache
EF	Emotional functioning
EPQ-R	Eysenck Personality Questionnaire – Revised
EQ-5D	The European Quality of Life scale
ETTH	Episodic tension-type headache
fMRI	Functional magnetic resonance imaging
GH	General health
GHQ-28	The General Health Questionnaire 28-items

GLM	General linear model
GON	Greater occipital nerve
GONB	Greater occipital nerve block
GP	General practitioner
HADS	The Hospital Anxiety and Depression Scale
HDI	The Henry Ford Headache Disability Inventory
HIT-6	The Headache Impact Test 6 items
HRQoL	Health related quality of life
ICHD	The International Classification of Headache Disorders
LATER	Linear Approach to Threshold with Ergodic Rate
LLR	Log likelihood ratio
MH	Mental health
MIDAS	The Migraine Disability Scale
MNI	Montreal Neurological Institute
MPQ	The McGill Pain Questionnaire
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MSQ	The Migraine-Specific Quality of Life Questionnaire
MSQOL	The Migraine-Specific Quality of Life measure
NHP	The Nottingham Health Profile
OUCH	The Organisation for the Understanding of Cluster Headache
ONS	Occipital nerve stimulation
PASL	Pulsed arterial spin labeling
PBC	The Pain Behaviour Checklist
pCASL	Pulsed continuous arterial spin labeling

PET	Positron emission tomography
PF	Physical functioning
QoL	Quality of life
rCBF	Regional cerebral blood flow
RE	Role emotional
REM	Rapid eye movement
ROI	Region of interest
RP	Role physical
RSES	The Rosenberg Self-Esteem Scale
SC	Superior colliculus
SF	Social functioning
SF-36	The Short-Form 36-items Health Survey
SNR	Signal to noise ratio
SPECT	Single photon emission computerised tomography
SPIC	Saccadic Programming and Instrumentation Computer
SUNA	Short-lasting unilateral neuralgiform headache with autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TAC	Trigeminal autonomic cephalalgia
TTH	Tension-type headache
VT	Vitality
WHO ICF	World Health Organisation International Classification of Functioning, Disability and Health

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Chapter 1 Introduction

Cluster headache (CH) is a rare primary headache disorder that is largely stereotypical, characterized by the presence of an excruciatingly severe unilateral pain accompanied by marked cranial autonomic symptoms. The disorder is said to be one of the most painful conditions known to mankind, with patients typically describing them as the worst pain they have ever felt (1). Female patients who have undergone childbirth invariably report that each attack is worse than labour pain (2). The intense nature of the pain often leaves patients feeling helpless and suicidal, and thus warrants early diagnosis and effective pain management. The headache can be quite disabling and can have a significant impact on patients' daily life, and subsequently on their health-related quality of life (HRQoL) (3, 4). Despite the numerous studies on CH to date, the pathophysiology of this disorder still remains poorly understood. Thus, this thesis adopted a mixed methods approach in the assessment of this disorder. With regards to treatment, a study utilizing functional magnetic resonance imaging (fMRI) is discussed in chapter 2, which intends to explore the central effects of the greater occipital nerve block (GONB), a well-known and used transitional form of treatment in CH. Chapter 3 discusses the use of saccadometry to study reaction times in CH patients to gain a wider understanding of the functional changes in this disorder. In chapter 4, the development and validation of the first health-related quality of life scale specific for CH sufferers is discussed, whilst from the same dataset, an assessment of the health-related quality of life in CH patients of episodic and chronic variant was made and is described in chapter 5. The final chapter (chapter 6) provides a general discussion of the findings from these studies, together with its limitation and

future direction. It is anticipated that via this approach, there will be a greater breadth of understanding of this highly disabling disorder, which in turn, may allow better management and future development of novel treatment strategies.

1.1 Cluster headache

1.1.a Diagnostic criteria

The revised International Classification of Headache Disorders (ICHD-3 beta) describes CH as a rare primary headache characterised by attacks of severe, strictly unilateral pain, which is orbital, supraorbital or temporal in location. Each attack typically lasts 15-180 minutes and may occur from once every other day to eight times daily (5). The diagnostic criteria of CH are presented in Table 1.1. Pain is often described as thermal or punctate in character, like 'a hot red poker in the eye' (6). CH is sometimes known as 'suicide headaches' as patients are known to develop suicidal ideations. The attacks are associated with marked ipsilateral cranial autonomic symptoms, including lacrimation, conjunctival injection, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis or eyelid oedema (7). Patients may also describe feelings of restlessness or agitation with the attacks, often reporting banging their head against the wall or floors. Attacks may be accompanied by migrainous symptoms such as nausea, vomiting, photophobia and phonophobia (8). Although ICHD-3 beta defines the headache as being strictly unilateral, up to 15% of patients may experience side shifting of their headaches between attacks, with each individual attack remaining strictly unilateral (1).

Table 1-1 The International Classification of Headache Disorders (ICHD-3 beta) Diagnostic Criteria for Cluster Headache (5)

A. At least 5 attacks fulfilling B - D.

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes if untreated.

C. Headache is accompanied by at least one of the following:

    1. ipsilateral conjunctival injection and/or lacrimation
    2. ipsilateral nasal congestion and/or rhinorrhoea
    3. ipsilateral eyelid oedema
    4. ipsilateral forehead and facial sweating
    5. ipsilateral miosis and/or ptosis
    6. a sense of restlessness or agitation

D. Attacks have a frequency from 1 every other day to 8 per day.

E. Not attributed to another disorder.

1.1.b Classification

Cluster headache typically occurs in bouts, which last for weeks or months and is termed as the episodic variant. These cluster bouts are separated by remission periods that can last months or years. On average, patients will experience bouts lasting 1-2 months, with 1-2 cluster bouts per annum. However, about 10 per cent of patients have chronic cluster headache, where they either have no remission periods for one

year, or their remission periods last less than a month (7). During its lifespan, CH can switch forms, with transition between the two variants being bidirectional.

1.1.c Epidemiology

Cluster headache has been estimated to affect about 1 in 1000 of the adult population, although a review of recent studies have indicated that its prevalence may be as high as 1 per 500 of the population, which the authors speculate may be because some patients with short attack duration or infrequent cluster bouts may not seek medical treatment (1, 9). The disorder has a predisposition for males, with a male: female ratio reported to be 2.5-7.2: 1 (1). Although it can present at any age, the usual age of onset is around 20-30 years (10). There have been reports of CH occurring in monozygotic twins, with an increased familial risk of having CH found in first-degree relatives of up to 39-fold. Meanwhile there is an 8-fold increased risk in second-degree relatives, suggesting a possible genetic component, although no particular genes have been identified to date (9, 11-13).

1.1.d Clinical features

The clinical features of CH are relatively stereotyped, although variations can occur. Pain is mainly focused in areas under the distribution of the ophthalmic division of the trigeminal nerve (V_1), although it may present in or radiate to other areas within the trigeminal nerve (V_2 or V_3) distribution (8, 14). Pain is usually rapid in onset, reaching peak intensity within minutes, and may either end abruptly or subside gradually. One of the striking features of CH is its tendency to exhibit circadian and circannual periodicity. The attacks tend to occur at specific times of the day, and patients often report having an attack an hour or so after falling asleep at night, during the first rapid eye movement (REM) sleep phase (1). Similarly, the cluster bouts tend to occur

around the same month/s of the year, with preponderance for onset in spring or autumn (1). During a bout, certain triggers such as alcohol, heat and the smell of volatile substances such as perfumes or solvents are known to trigger attacks (6, 15). Nitroglycerin is another well-known trigger and is commonly used to precipitate attacks in experimental studies (16-19).

1.1.e Pathophysiology

The pathophysiology of CH is still incompletely understood, however several theories have been put forward in an attempt to explain it. Taking into account the trigeminal distribution of the pain and the associated autonomic symptoms, the neurological pathways involved are presumed to be the trigeminal, cervical (C2 and C3) sensory nerves and the parasympathetic system routed mainly via the otic, ciliary and pterygo palatine ganglia (via ninth, third and fifth cranial nerves respectively) (1, 20). CH was initially thought to be a vascular headache originating from inflammation within the cavernous sinus (6, 20). The resulting venous stasis caused pressure on the trigeminal nerve, which simultaneously activated the intersecting parasympathetic and sympathetic nerves, eliciting pain and the autonomic symptoms respectively (6, 20-22). Moreover, the efficacy of Sumatriptan, a 5-hydroxytryptamine agonist, which has vasoconstrictive effects in aborting these attacks further supported this notion (23, 24). However, this theory could not explain the circadian rhythmicity of the attacks.

The circadian and circannual periodicity of CH indicated a possible central nervous system involvement, with the human biological clock implicated as a potential site. This is situated in the suprachiasmatic nucleus within the hypothalamus, which is also responsible for regulating hormonal activities. Interestingly, studies have shown hormonal abnormalities in CH patients, such as a significant decrease in plasma

testosterone levels in male CH patients and a reduced response to thyrotropin-releasing hormone (25, 26). Furthermore, a blunted nocturnal peak in melatonin, a circadian system biomarker, has been found in patients with CH (27, 28). This concept of a possible central nervous system involvement has therefore led to several neuroimaging studies in this disorder.

1.1.f Neuroimaging studies in cluster headache

i Nitroglycerin: a reliable trigger?

The first positron emission tomography (PET) study on CH was performed by Hsieh and colleagues using [^{15}O]butanol as the tracer for regional cerebral blood flow (rCBF) on a limited sample size (17). They studied four right-handed patients during their active cluster period, two with right-sided and two with left-sided attacks. The headaches were elicited within 18-35 minutes of administration of 1 mg sublingual nitroglycerin and successfully terminated following subcutaneous administration of Sumatriptan (17). A 100 mm visual analogue scale (VAS) was used to enable patients to rate their headache intensity. Each patient underwent six scans: two at baseline (10 minutes apart), one following nitroglycerin administration, two following onset of the CH (10 minutes apart) and lastly following pain relief with Sumatriptan. The authors reported that there was a preferential role of the right, non-dominant hemisphere, especially the anterior cingulate cortex, in the affective-cognitive processing of pain in these patients (17). Other brain areas consistently involved in the central processing of pain were activated, but there were no changes seen in the brainstem or diencephalon (17). Furthermore, they found a marked increase in rCBF in the cavernous sinus region, which suggested a possible blood flow disturbance and hence a role of the

cavernous sinus in the pathophysiology of CH (17). However, this hypothesis is challenged following further studies, as will be discussed in the following section.

May and colleagues performed a similar study on 17 CH patients (18). Nine of them were in their active cluster period, whilst eight who were in a remission phase acted as controls. In this study, the headaches were provoked by inhalation of 1.0-1.2 mg nitroglycerin, although one patient developed attacks spontaneously in the scanner (18). $H_2{}^{15}O$ was used as a tracer and each patient underwent 12 or 13 consecutive scans with VAS ratings. All patients reported similarity of the triggered attacks to their usual headaches. Increases in rCBF were reported in the cerebellum, bilateral anterior cingulate cortex and insula, the contralateral posterior thalamus and ipsilateral basal ganglia in these patients (18). A distinctive finding from this study was increase in rCBF in the ipsilateral hypothalamic grey, which was not seen in the control group (18). This implies that this area is specifically activated only during a CH attack, therefore providing substantial evidence of hypothalamic involvement (18). An increase signal in the cavernous sinus region of patients who were in their active cluster period was seen, with no differences noted between the spontaneous and evoked attacks (18).

Sprenger and colleagues presented an incidental case of a spontaneous cluster attack in a patient whilst undergoing $H_2{}^{15}O$ PET scanning to study the effects of deep brain stimulation (29). The areas showing increases in rCBF were comparable to the earlier studies done with nitroglycerin-induced CH (17, 18). Hence, the authors concluded it was unlikely that the use of nitroglycerin to trigger the attacks confounded the imaging data (29).

ii The cavernous sinus theory

Cluster headache has long been coined a vascular headache with the cavernous sinus being implicated as the focal generator of symptoms. Early studies looking at the cerebral blood flow of patients with CH reported inconsistent results, with some reporting an increase, some a decrease whilst others showed no changes in cortical blood flow (16, 30, 31). Gawel and colleagues studied six CH patients using gallium SPECT (single photon emission computerised tomography) during an active cluster period (32). There was an increased activity seen in the parasellar region in three of the cases, however, due to the limited resolution, the exact location could not be defined, but the authors believe that it lies in close relation to the cavernous sinus (32). On the contrary, no definite pathology was found in the cavernous sinus region in a magnetic resonance imaging (MRI) study of 14 CH patients (33). A repeat gallium SPECT study done on 30 CH patients and seven migraineurs showed the marked activity within the parasellar region was not limited to CH only but was also seen in migraine (34). Likewise, Schuh-Hofer and colleagues found no evidence for an inflammatory process in the cavernous sinus of six CH patients investigated using ^{99m}Tc-human serum albumin and SPECT (35). These findings thus question the role of the cavernous sinus as the pathophysiological focus in CH.

Despite the consistent findings of significant increases in rCBF within the cavernous sinus region in PET studies, experimental pain studies have also reported similar findings (36). A $H_2{}^{15}O$ PET study performed observed the effects of cranial pain elicited by capsaicin (36). Seven healthy subjects had a small amount of capsaicin injected to their forehead, in an attempt to elicit pain of the ophthalmic division of the trigeminal nerve. Increased rCBF was observed bilaterally in the anterior insula, the

ipsilateral anterior cingulate cortex, the contralateral thalamus and bilaterally in the cerebellum as well as in the cavernous sinus (36).

Similar findings were reported by May and colleagues who performed a magnetic resonance angiography (MRA) study in addition to the $H_2{}^{15}O$ PET study above (19). Four volunteers had capsaicin subcutaneously administered to the forehead to elicit pain. The patient who developed the spontaneous cluster attack during the $H_2{}^{15}O$ PET study was also included. A significant increase in blood flow was observed in the ipsilateral internal carotid artery in all subjects (19). The fact that there is increased activity in the cavernous sinus in experimental pain, during cluster attacks and in migraineurs implies that this activation is not specific to CH (19). The vascular changes seen are thus more likely to be an epiphenomenon in response to the trigeminal pain, rather than an initiator of the attacks, hence dispelling the cavernous sinus hypothesis (19). Moreover, no activation of the hypothalamus was reported in the experimental pain study, further suggesting its specificity to CH (36).

iii The hypothalamic hypothesis

In the wake of the direct evidence found for a possible hypothalamic involvement, other neuroimaging modalities have been used which aims to shed further light to this hypothesis. Morelli and colleagues performed the first blood oxygen dependent level (BOLD) fMRI study on four patients with episodic CH (ECH) (37). The patients had a regular recurrence of their attacks, thus their scans were timed accordingly to allow spontaneous attacks to be captured. Significant activation in the ipsilateral hypothalamic grey matter was observed, though any inferences should be treated with caution due to the small sample size (37).

May and colleagues performed a voxel-based morphometric analysis on MRI scans of 25 CH patients and 29 healthy controls (38). Fourteen of the CH patients were in an

active bout, whilst 11 patients were in their remission period. A significant increase in grey matter density localised to the inferior posterior hypothalamus was found bilaterally in these patients compared to controls. No difference was detected between patients with active headache and in the headache-free state, indicating that these changes are specific to the disorder (38). However, a repeat study by Matharu as part of his PhD thesis failed to replicate these findings, and he identified several limitations of the original study (39). These included methodological issues related to data processing and analysis, such as an outdated version of software used, failing to correct for motion artefacts and incidental pathology, and patients and controls not correctly matched for age and gender (39).

Lodi and colleagues performed a proton magnetic resonance spectroscopy (^{1}H-MRS) localized to hypothalamic gray matter bilaterally, on 26 pain-free patients with CH (40). Biochemical levels of *N*- acetylaspartate (NAA), creatine-phosphocreatine (Cr) and choline (Cho) were assessed. The level of NAA, a neuronal biomarker was permanently reduced in the hypothalamus of these patients, with such abnormalities usually identifiable in pathologies like stroke, degenerative disorders and multiple sclerosis (40). Similar findings were reported from another proton magnetic resonance spectroscopy study of 47 ECH patients (41). In addition to a reduction in NAA/Cr, a change in the Cho/Cr levels was also detected (41). These neurochemical changes are consistent with the increased grey matter density and a hypothalamic dysfunction in patients with CH, thus providing further evidence for the central role of the hypothalamus in this disorder.

However, it has recently been argued that the hypothalamic derangements observed in CH may not be specific to the disorder (42). Hypothalamic activation and structural alterations are not exclusively observed in CH but can also be found in other primary

headache disorders including migraine, hemicrania continua and hypnic headache (42-45). In migraine, bilateral hypothalamic activation was observed during spontaneous migraine attacks using PET imaging, whereas in hemicrania continua, the activation was observed contralateral to the side of pain, therefore suggesting that this region may be simply involved in the general processing of pain (44, 45). A VBM study in hypnic headache reported a decrease in grey matter volume within the posterior hypothalamus (43). Whilst these observations question the specificity of hypothalamic involvement in CH, the converging evidence from neuroimaging, neuroendocrine and genetic studies, taken together with the clinical presentation of the disorder, and the emergence of deep brain stimulation (which will be discussed below), highlights the importance of the hypothalamus in CH pathophysiology.

1.1.g From neuroimaging to treatment modality

Neuroimaging studies have provided considerable insight into the pivotal role of the hypothalamus in the pathogenesis of CH. As previously described, this has brought about advancements in treatment modalities, namely deep brain stimulation (DBS), which has been reported to be beneficial in medically-intractable patients (46). $H_2{}^{15}O$ PET studies performed on 10 CH patients with implanted hypothalamic DBS electrodes demonstrated that stimulation induced changes in rCBF in cerebral areas normally involved in the pain-processing network and in acute CH attacks (47). In particular, increases in rCBF were reported in the ipsilateral hypothalamic gray (the site of the stimulator tip), the ipsilateral thalamus, somatosensory cortex and precuneus, the anterior cingulate cortex, and the ipsilateral trigeminal nucleus and ganglion. Reductions in rCBF were observed in the middle temporal gyrus, posterior cingulate cortex, and contralateral anterior insula (47). There was no evidence found for an antinociceptive effect or a pure inhibition of hypothalamic activity as the mode

of action of DBS in CH, thus suggesting the possibility of a yet unknown functional modulation of the processes involved in pain generation (47).

1.1.h Management

The majority of patients with CH receive pharmacological treatment for their headaches, and only a small proportion of chronic CH (CCH) patients that are deemed medically intractable are offered surgical interventions. The three main categories of medical management of this disorder are acute, preventive or transitional therapies. As the name suggests, acute or abortive treatment is aimed at aborting each individual attack and should be given at the onset of an attack. Preventive medications are used to suppress attacks during a bout and ideally to achieve and maintain remission whilst the patient is still in a bout. They generally need to be titrated to an optimum dose and thus their beneficial effect may not become apparent until after a few days to weeks of starting the medication. Transitional treatments can therefore be very helpful during this period as they can bridge this gap by rapidly suppressing the attacks, although they are only generally effective for a few days to weeks.

i Medical management

a Acute treatments

The acute treatments of choice in CH include inhalation of high-dose and high-flow-rate oxygen (100% at 7-15 L/min via a non-rebreathing face mask) and subcutaneous Sumatriptan 6mg, which can usually abort an attack within 15-30 minutes. However, there is also evidence for efficacy of intranasal triptans (Sumatriptan 20 mg or Zolmitriptan 5mg and 10 mg) or oral Zolmitraptan 10 mg (only in ECH) as alternate abortive treatments (48, 49).

b Preventative treatments

The prophylactic treatment of CH is largely empirical based, due to the limited numbers of controlled trials to provide evidence-based guidelines and the lack of understanding of its pathophysiological basis (48-52). The first drug of choice is Verapamil (50, 51), due to its efficacy and relative safety profile, which is used clinically at dosages of 240 - 960 mg daily, with close electrocardiographic monitoring (48). Randomised-controlled trials and open-label studies have been reviewed and Lithium, Topiramate, Methysergide, Sodium Valproate, Gabapentin, Melatonin and Baclofen have been reported to be efficacious in CH (50, 52).

c Transitional treatments

Transitional therapy allows a short-term solution in controlling the CH attacks whilst waiting for the preventive medication to take effect, and can thus be thought of as a short-term preventative. Theoretically, it should be quick-acting, providing almost immediate pain relief and should last long enough to allow the preventive medication to be increased to an effective level (53). On the other hand, it can also be used in patients who remain refractory to the other medications or are unable to tolerate their adverse effects (54). The types of transitional treatments available for CH are short courses of oral corticosteroids and injectable treatments including greater occipital nerve blocks (GONBs) and multiple cranial nerve blocks.

- **Greater occipital nerve blocks**

The GONB is one of the most common peripheral nerve block used in headache management. It involves a simple procedure with minimal side effects and has been suggested to provide pain relief in a number of headache disorders, including CH (55, 56). However, although the technique has long been used in clinical practice, its mechanism of action is poorly understood.

A proposed hypothesis is centred on the convergence between the cervical and trigeminal systems at the level of the trigeminal nucleus caudalis (53, 56-58). The GON is the main sensory nerve of the occipital area, deriving most of its fibres from the C_2 dorsal root (59). Blocking the GON is thought to reduce the cervical afferent input to the nucleus, which then modulates central processes and alters nociceptive processing, with possible interruption of the trigeminal autonomic reflex pathway (53, 56-58). This functional connectivity or convergence of the nociceptive trigeminal and cervical afferents is supported by a decrease in nociceptive blink reflex and increased R2 latency on the injection side, following an occipital nerve blockade in CCH patients and headache-free controls (55, 60). Furthermore, an experimental trial of a GONB containing sterile water induced immediate pain not only over the injection site but also projecting to unilateral areas innervated by the ophthalmic division of the trigeminal nerve (V_1), with associated cranial autonomic features (61). Within the clinical setting, CH patients also often report of having associated neck tenderness or stiffness with their headaches or vice versa.

A randomized, double-blind, placebo-controlled study has reported 11 out of 13 (85%) CH patients were attack-free one week following the procedure, compared to none in the placebo group, with eight patients (61%) remaining headache-free at 4 weeks (62). In another study that included 14 CH patients, 64% had either a good or moderate response to the block and remained attack-free for 3-70 days (53). Afridi and colleagues performed an audit study of GONBs administered to 101 patients with different forms of primary chronic daily headache, including 19 CH patients, and found that 53% of patients had complete pain relief whilst 16% had partial pain relief after being administered a GONB (56). Of the CH patients, 59% had either a complete or partial response to the GONB. Leroux and colleagues carried out a randomized,

double-blind, placebo-controlled trial and showed that in 43 CH patients who have frequent daily attacks, giving repeated GONB with steroid (cortivazol) is an effective transitional therapy (63). In their study, there was a reduction in the number of daily attacks, reduced need for Sumatriptan injections and Verapamil and a higher patient satisfaction score in those receiving the steroid injection compared with placebo (63). A retrospective, open-label study confirmed the efficacy of 121 GONBs given to 60 ECH and CCH patients, with almost 80% of infiltrations resulting in a positive response; 43.7% showed a complete response, with effect lasting an average of 3.5 weeks (64). Our group recently carried out a prospective study on a large cohort of CCH patients (83 patients) and found that 57% had a positive response lasting a median of 21 days (range 7 – 504 days). Of those that responded to the GONB, 42% had a complete response whilst 15% had a partial response with ≥ 50% improvement in headache characteristics (frequency, duration or severity). Furthermore, we showed that repeated GONB given every three months produces a consistent and reproducible response in a subgroup of responders (65). These positive findings thus suggest that GONB is an effective transitional treatment in CH.

d Surgical management

In view of the trigeminal pain and cranial autonomic features characteristic of CH, a number of surgical interventions targeting the trigeminal and parasympathetic pathways have been tried over the years. These procedures are mostly ablative or destructive, with sparse benefit, and include glycerol or local anaesthetic injections to the Gasserion ganglion, partial or complete sectioning of the trigeminal root, radiofrequency rhizotomy of the Gasserion ganglion and microvascular decompression (66, 67). However, technological advances and knowledge of possible underlying mechanisms in CH, as discussed above, has led to the advent of

neurostimulation procedures, which are non-destructive and have been shown to have good efficacy. These have considerably broadened the arsenal of therapeutic options available and include occipital nerve stimulation, hypothalamic deep brain stimulation and sphenopalatine ganglion stimulation (46, 66-69).

Therefore with regards to treatment, there is accumulating evidence for the efficacy of the GONB in CH, although little is known about the mechanisms relating to its treatment effect. Previous neuroimaging studies in CH have provided useful insights into the structures that may have pivotal roles in the pathophysiology of the disorder. Hence, similarly, it may also be a useful modality in understanding the effects of the GONB in this patient group.

1.2 Saccadometry and cluster headache

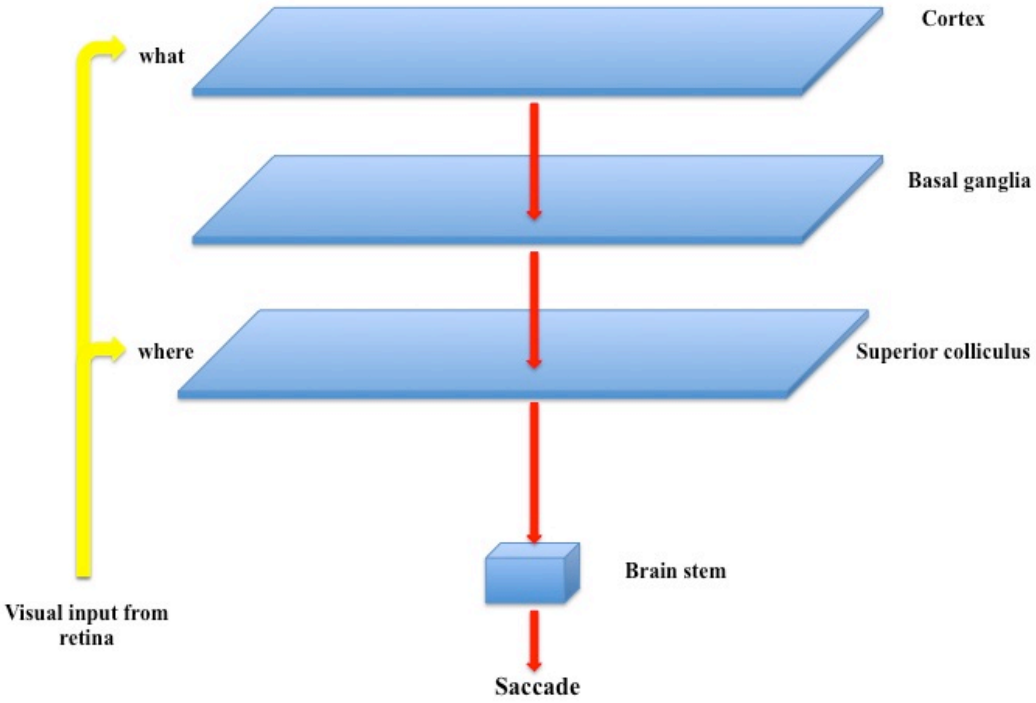
Although our understanding of CH has improved over the years, its medical management is still empirically based, whereas surgical interventions have been based on research studies that provided evidence of structures likely to be involved in its pathogenesis. Since the former remains the mainstay for management of this disabling disorder, there is clearly a need for better understanding of the underlying pathophysiology to allow improvement in its management. Saccadometry- the study of saccadic eye movements has been utilised in a variety of neurological disorders including Huntington's and Parkinson's disease to gain insight into the effects of those conditions on neural function (70-73). Saccades are the spontaneous rapid eye movements made to targets of interest within our visual environment (73). They are the fastest and most frequent movements produced by the body- the eyes make two or three saccades per second (74). Since saccadic movements are highly stereotyped, useful information can be gained by studying abnormalites within them due to disease

states (74). One of the parameters used in describing saccadic movements is its latency, which is the time taken from the onset of a stimulus to the onset of eye movement, or in other words, reaction time. Saccadic latencies vary randomly from trial to trial, and therefore a meaningful analysis should take into account this variation by reporting not only its mean or median value but also the whole distribution, which can only be achieved from large datasets (75). The development of a portable head mounted saccadometer now permits fast acquisition of such large datasets, enabling up to 100 saccades to be collected over a two to three minute period (73). Furthermore, head restraints are not required, meaning that studies can now be easily performed outside of the laboratory setting (73).

1.2.a Generation of a saccade

In theory, saccadic latencies should be very short, around 60-80 milliseconds, since it reflects the time taken for a visual stimulus to elicit an oculomotor response (Figure 1.1). Visual input from the retina is conveyed to the superior colliculus (SC) - a midbrain structure that is responsible for coding information about 'where to look', which triggers the oculomotor nuclei within the brainstem to initiate movement. However, in reality, saccadic latencies usually last up to three times longer, because the visual information are also projected to and further analysed in cortical areas. These structures are mainly tonically inhibitory and hence, the delay in reaction time is due to the descending inhibitory inputs from these higher structures to the SC, whilst a decision is made on 'what to look at', and as such reaction time is fundamentally decision time (73).

Figure 1-1 A schematic illustration of saccadic control showing the neural pathways involved in generation of saccades. The shortest pathway for generation of a saccade is from the retina-superior colliculus-brainstem-oculomotor muscle, which should last 60-80 msecs. However, in reality, saccades last much longer (about three times longer) as visual input from the retina is conveyed to the cerebral cortex via the lateral geniculate nucleus in the thalamus, where decisions are made on what to look at. The superior colliculus receives descending inputs from the cerebral cortex and basal ganglia, which then triggers the brainstem saccade generator to make a saccade. Adapted from Carpenter (**http://www.cudos.ac.uk/later.html**)

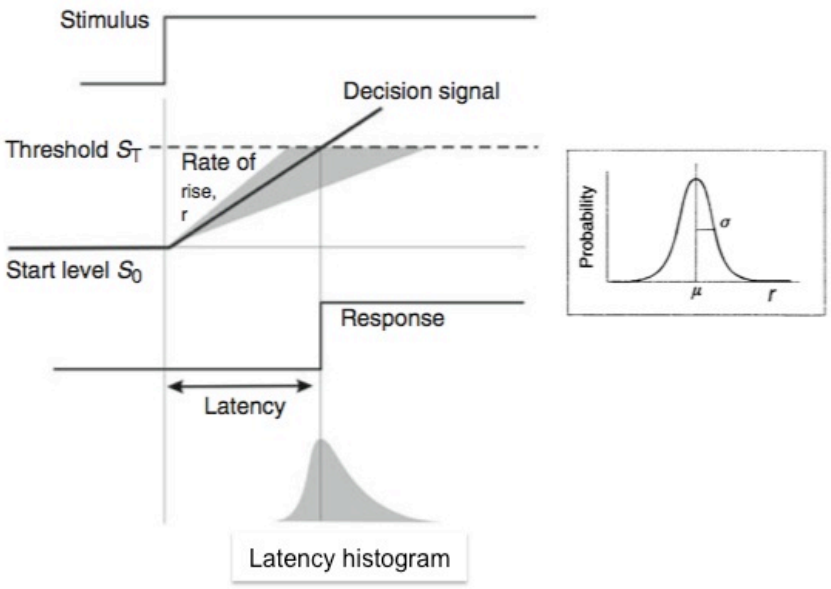


1.2.b The LATER model

Carpenter (1995) (76) developed the LATER model (Linear Approach to Threshold with Ergodic Rate) to describe the decision-making process involved in the generation of saccades. He suggested that a decision signal S, rises linearly at a constant rate r, in response to incoming information from the stimulus, until it reaches a criterion or threshold level S_T, for triggering initiation of a response (77). Since latency or reaction time and rate is reciprocally related, then if the rate of rise r, varies from trial

to trial as a normal distribution, with mean μ and variance σ^2, then this explains the recinormal distribution of latency, as explained below (76).

Figure 1-2 Diagram illustrating the LATER model which describes the decision-making process in the saccadic generation. A decision signal S, rises linearly at a constant rate r, in response to incoming information from the stimulus, until it reaches a criterion or threshold level S_T, for triggering initiation of a response. When plotted on a histogram, latency is positively skewed (shaded area), however its reciprocal, rate (r) varies from trial to trial as a normal distribution, with mean μ and standard deviation σ (inset). Adapted from Chandna and colleagues (75).

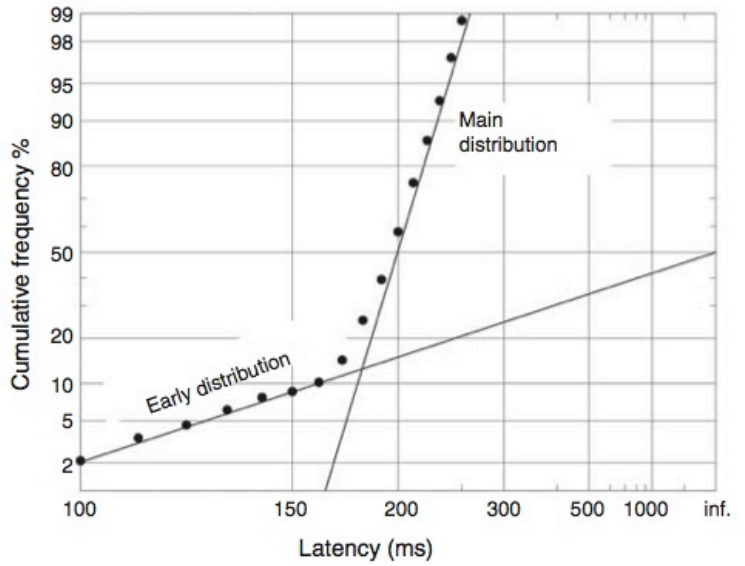


1.2.c Reciprobit plots

As previously mentioned, saccadic latencies are highly variable from trial to trial and thus will always have a skewed distribution (77). However, this can be normalised by applying a reciprocal transformation (yielding a *recinormal* distribution), which when plotted on a cumulative histogram with latency on a reciprocal scale and probability on a probit scale, will transform a normal distribution to a straight line, as shown in

Figure 1.3. This plot is known as a *reciprobit* plot as it combines both reciprocal and probit scales (73, 77). The line can be defined by its intercept at the 50% axis and its slope, which is the mean and standard deviation of latency respectively. Occasionally, there is a sub-population of fast (early) saccades that lie on another line of shallower slope, which can be described by its standard deviation, σ_E (77).

Figure 1-3 Graph showing a reciprobit plot with latency on a reciprocal scale (x-axis) and cumulative probability on a probit scale (y-axis), illustrating that the reciprocal of latency follows a normal distribution. A small subpopulation of early or very fast saccades is generated by some individuals, which lie on another line with shallower slope. Reprinted from Chandna and colleagues (75).



1.2.d Saccadic reaction time in headache disorders

To date, there have been only studies of saccadic reaction time in migraine, whereas other headache disorders have not been evaluated. The interest in studying saccadic eye movements in migraineurs in this past decade arose following evidence from

genetic and neuroimaging studies that suggested the cortical areas implicated during a migraine attack were also associated with saccadic control (78-80). These authors therefore hypothesized that this would be reflected by an abnormal saccadic behaviour, but they failed to provide any evidence for abnormal saccadic eye movements in migraineurs with and without aura, compared to headache-free controls (79, 80). Similarly, no significant differences in saccadic latency between migraine groups were found by Cambron and colleagues (78). However, compared to controls, they found significant differences in several parameters of saccadic latency. A possible reason for this may be due to methodological differences, whereby the latter study included three different saccadic tasks that were more challenging compared to the earlier studies, and that they looked at the whole distribution of latency (78). In particular, they found a significant difference in the standard deviation of latencies in the "pro-overlap" and "pro-gap" tasks. In the "pro-overlap" task, the subject is instructed to look as quickly as possible to an extra stimulus, whilst the original fixation point stays on, whereas in the "pro-gap" task, there is a short gap between the fixation point disappearing and the stimulus appearing. The authors suggested that this difference reflects the high variability in the parietal cortex-collicular input, which subsequently reflects changes in visual attention (78). Moreover, there were significantly more errors made in the "anti-saccade" task, where subjects had to move their eyes in the opposite direction to the stimulus, suggesting a dysfunction in inhibitory control of reflexive saccades involving the prefrontal or cingulate cortices (78). Conversely, a recent study using a different task found that migraineurs had reduced variability in their saccadic latency compared to controls, and had less incidence of early saccades (75). The authors hypothesize that these differences that were restricted only to variability of saccadic latencies, without significantly affecting

its mean, may reflect changes in noradrenergic activity in migraineurs, thus ultimately providing insight into the underlying neural mechanisms in migraine. Furthermore, they speculate that the high discriminative power of saccadometry in this disorder may potentially lead to its use as a diagnostic tool within the clinical setting (75). Due to the discrepancies in the findings of saccadic reaction time distributions from these studies, further work is clearly needed to clarify the nature and scope of any impairment.

Saccadometry has therefore allowed some understanding of the possible functional changes associated with migraine. However, there have been no studies examining saccadic reaction time in other headache disorders, in particular CH, which could potentially characterize its neurological function and allow better understanding of its pathophysiological basis.

1.3 Quality of life in primary headache disorders

Quality of life (QoL) is a measure of an individual's general well-being, whilst health-related quality of life (HRQoL) measures the impact of an illness on the patients' physical, emotional and social functioning (81). Over the past decades, the importance of measuring HRQoL in patients with chronic disorders has become an area of interest in clinical practice, as it provides the patient's subjective experience of the impact of their disorder, incorporating the biopsychosocial model of health (81, 82). Within the headache field, much of the work relating to HRQoL has focused mainly on migraine, as it is one of the most frequent primary headache diagnoses. Despite the lack of any physical abnormality in headache disorders, the nature of the attacks with their recurring pain and associated symptoms often influences the patients' ability to function normally. Indeed, the World Health Organization (WHO) in their Global Burden of Disease study conducted in 2010 reported that tension-type headache and

migraine are the second and third most common diseases in the world respectively. Migraine ranked highest amongst all neurological diseases and in seventh place as specific causes of disability worldwide (83).

Several conceptual models of HRQoL exist that serves to describe the underlying dimensions or elements that are defined by and included within this construct. The three most common models used in the literature are the Wilson and Cleary, Ferrans and colleagues, and the World Health Organisation International Classification of Functioning, Disability and Health (WHO ICF) models (84). Wilson and Cleary integrates biological and social science paradigms into their HRQoL model, which are divided across five domains, namely biological/physiological variables, symptom status, functional status, general health perceptions and overall quality of life, with characteristics of the individual and their environment feeding into and influencing the four latter domains (84, 85). The authors proposed that measures of health exist on a continuum of increasing complexity from the biological/physiological domains on one end to the general health perceptions on the other end (85). This model was then revised and simplified by Ferrans and colleagues, whilst still retaining the five original domains, and suggested that individual and environmental characteristics also influences biological function (86). Meanwhile, the WHO ICF model provides a description of health states, in particular the interaction of functioning and disability on health, which serves more as a classification framework rather than as a guide for HRQoL (84, 87).

Inclusion of HRQoL as an outcome measure is increasingly recognized in clinical trials and in cost-effective analysis of interventions, as is its use in routine clinical practice for monitoring purposes. However, there are a number of challenges that can be encountered in measuring HRQoL. This includes choosing a suitable instrument to

assess HRQoL for a particular disorder, with straightforward data analysis and interpretation, and that ideally allows incorporation of findings into clinical decision making (88). As the underlying aim of measuring HRQoL is to gain a patients' perspective of their illness on their wellbeing, HRQoL measures should be based on and reflect the patients' point of view, rather than purely those of clinicians or health care professionals (88, 89). HRQoL measures should therefore be designed with patients in mind, as discrepancies may exist on areas of life or wellbeing that are deemed important by them compared to clinicians, thus ensuring that the items covered in the measure truly reflects how the disorder affects their lives (90, 91). HRQoL measures must be valid, reliable, and responsive, as well as be simple to administer, score and interpret to have clinical usefulness (88, 90-92).

Over the years, various instruments have been developed to evaluate HRQoL, which include generic and disease-specific measures. Generic HRQoL instruments can be used to measure HRQoL in many different disorders, allowing comparisons with other medical conditions and with healthy controls (48, 93). Whilst these measures provide a good overview of the impact of a disease on HRQoL, the general broad nature of the items within these instruments limits their ability to detect changes that are specific to a particular disorder and they may not be sensitive enough to detect small, clinically important changes in HRQoL, for example following treatment in a particular disorder (90-92). Hence, disease-specific measures have been developed to overcome these shortcomings, and thus includes items that are important and relevant only to patients suffering from the particular disorder being studied (90-92).

1.3.a Generic HRQoL instruments

The most frequently used generic HRQoL measures include the Short Form-36 item (SF-36) Healthy Survey, the Nottingham Health Profile (NHP) and the European Quality of Life (EQ-5D) scales.

The SF-36 Health Survey is a generic HRQoL measure with excellent reliability and validity (94). It contains 36 self-administered items, measuring functions in eight domains. Physical functioning (PF) has ten items measuring the ability to perform a variety of physical activities. Role-physical (RP) measures the extent to which physical health interferes with usual daily activities (four items). Bodily pain (BP) assesses the extent of bodily pain in the past four weeks (two items). General health (GH) contains five items and is an overall rating of health in general. Vitality (VT) measures general energy over the past four weeks (four items). Social role functioning (SF) assesses the extent to which health interferes with normal social activities (two items). Emotional role functioning (EF) has three items measuring the extent to which emotional problems interfere with usual daily activities, and mental health (MH) is a measure of general mood in the past four weeks (five items). The subscales are scored on a scale of 0 to 100, with higher scores indicating better HRQoL in the domain being measured (94).

The Nottingham Health Profile (NHP) is a 45 item self-administered instrument divided into two parts. The first part assesses areas related to health, including sleep, physical mobility, energy, pain, emotional reactions and social isolation, whereas the second part assesses areas of daily life most often affected by health. These include paid work, household chores, social life, personal relationships, sex life, hobbies and interest, and holidays (95).

The European QoL (EQ-5D) Questionnaire is a generic measure of current health status. It consists of five domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of these domains has three possible response options; no problems, some or moderate problems or extreme problems. In addition, there is a visual analogue scale, with 0 being the worst imaginable and 100 being the best imaginable current health state (96). Recently, the EQ-5D has been revised in an attempt to improve the instruments' sensitivity (97). The revised scale includes five possible response options for each item (EQ-5D 5L); no problems, slight problems, moderate problems, severe problems and unable to/extreme problems, and has been shown to be a valid extension to the previous 3-level system (98).

1.3.b Migraine-specific HRQoL instruments

Migraine-specific HRQoL scales have been developed to measure the unique symptoms or areas of life that may be affected in this patient group. This includes the Migraine-Specific Quality of Life scale (MSQOL) (99), the Migraine-Specific Quality of Life Questionnaire (MSQ) (100, 101), and the 24-hour Migraine Quality of Life Questionnaire (24-hr-MQoLQ) (102).

The MSQOL is a 20-item questionnaire covering three domains; avoidance, relationships and feelings (99, 103). The 24-hr-MQoLQ contains 15 items measuring five domains associated with an acute headache; work functioning, social functioning, energy/vitality, migraine headache symptoms and feelings and concerns (102). Meanwhile, the MSQ v2.1 is a 14-item measure, divided across three domains; role restrictive, role preventive and emotional functioning. Role restrictive contains seven items assessing the degree to which the performance of normal activities is limited by migraine, whereas role preventive (four items) measures the degree to which the performance of these activities is interrupted by migraine. Three items assess the

emotional impact due to migraine (emotional functioning). This questionnaire has been shown to have good internal consistency and construct validity (101). The total possible score ranges from 14 to 84, with higher scores indicating poorer HRQoL.

Furthermore, a number of headache disability scales that assesses impact and disability due to headaches are available, which include the Migraine Disability Assessment Scale (MIDAS), the Headache Impact Test (HIT-6) and the Henry Ford Headache Disability Inventory (HDI). Although disability and HRQoL are independent constructs, they are closely related and assessment of disability are often included as part of HRQoL measures (104).

1.3.c HRQoL by headache diagnoses

i Migraine

Studies assessing HRQoL in migraine demonstrated that, overall, migraineurs had significantly diminished HRQoL in both physical and mental health domains of the SF-36 compared to healthy controls (105-119). Physical functioning, social functioning, mental health and role disability due to emotional problems were the domains found to be least affected (106, 109, 111, 113, 115, 119). No differences were reported in HRQoL between migraine subtypes, namely migraine with aura, migraine without aura, and migraine with and without aura (107). The tendency of having a fairly intact mental health score had led some authors to suggest that physical impairment has a greater role in influencing poorer HRQoL than mental impairment (109, 120). However, whilst migraineurs have reported difficulties in physical activities such as mobility, driving, lifting and carrying objects, the majority report their impairments are related to mental functions (107, 113, 121-123), with 87% reporting difficulties with activities requiring mental effort, compared to 47%

reporting limitations of physical activity (124).

Taking into account that migraine usually affects individuals during their productive years, two studies evaluated HRQoL impairment in groups of employed individuals with migraine, namely nurses and French workers. The nurses suffering from migraine showed lower HRQoL compared with non-headache participants, especially in the physical role and bodily pain subscales, which are sensitive to headache severity. Consequently, this affected their work, leading to missed workdays, arriving late, and reduced function and productivity at work (105). Conversely, a comparative study among French workers showed that absenteeism among migraine sufferers was not statistically different from controls, although performance was greatly reduced (106).

This goes in line with the general finding that migraine sufferers tend to attend school or paid work despite having a headache, with more days of reduced productivity at school or work than actual days of missed activity (111, 113, 122-128). Studies utilizing the MIDAS and HIT-6 questionnaires have found that the majority of migraineurs (up to 70%) (111, 122, 125, 126, 129-133) were moderately to severely disabled or impacted by their headaches (MIDAS and HIT-6 grades III and IV), with a trend of more missed days reported for household work, followed in order by family, social and leisure activities and school or paid work respectively (134, 135). Days of reduced productivity in household chores (with productivity reduced by at least half) were also greater than in school or paid work (111, 113, 122, 124-128, 136). Hence, reduced work productivity and absenteeism amongst migraineurs are well reported, and this can have a substantial economic impact (105, 137-139). Moreover, even between attacks, the individual's well-being is impaired, which can be disruptive on social and family relationships.

This tendency of missing family time over paid work can lead to disruption in family relationships. Ruiz de Velasco and colleagues found this to be a central issue raised by patients and relatives in their study, whereby both parties reported that family environment was the area most affected by migraines (123). Patients and their spouses also expressed their concern regarding the impact of migraines on emotional development of their children (123). Indeed, a study exploring the relationship between maternal migraine and child functioning found that migraine may be related to dysfunctional parenting patterns, with the risk of parent-child reversal roles and inappropriate parents' expectation of their children increasing as a mother's migraine becomes disabling (140).

With regards to migraine amongst the paediatric and adolescent population (116, 141-143), there was an overall impairment in HRQoL domains. Adolescents reported more impairment in school functioning, whereas social functioning was reportedly more impaired in younger children (aged 5-7 years) (141, 142). Adolescent autonomy and coping mechanisms plays a significant role in determining their HRQoL; the more able a child is in coping with their pain, the better their HRQoL. Moreover, having a successful adaptive family routine, whereby families adapt and organize their daily activities in a positive way for all members, predicts a better outcome for HRQoL (144, 145).

In view of the emotional and mental impairments associated with migraine, much attention has been focused on the association between psychological wellbeing and HRQoL (109, 110, 115-117, 142, 146-151). These studies showed that most migraineurs exhibited anxiety and/or depressive symptoms, and comorbidity with both anxiety and depression was positively correlated to headache-related disability (115, 147). These psychiatric disorders have a negative influence on HRQoL

independent of each other; however migraineurs with combined anxiety and depression have significantly poorer HRQoL scores, with the greatest impact being on the mental health domains (110, 115, 116). The presence of these affective disorders also affects perceived migraine, treatment satisfaction and efficacy (115). Conversely, Mula and colleagues reported no differences in HRQoL scores between migraineurs with and without comorbid psychiatric disorders (150). Moreover, it has been suggested that the psychological response to severe migraine, particularly catastrophizing, has a greater impact on HRQoL impairment than the mere presence of comorbid anxiety and/or depression (149).

The HRQoL of migraine patients has been compared to those with other chronic conditions to allow a better overview of the degree of impairment in this disorder. In comparison to asthmatics, migraineurs scored significantly lower on social functioning, role emotional, mental health, bodily pain and vitality domains. However, compared to patients with chronic musculoskeletal pain and juvenile fibromyalgia, migraineurs had a better overall HRQoL (107, 142). Similarly, children with primary headache disorders scored significantly worse on all aspects of HRQoL, except physical functioning and general health perception subscales, when compared to children with asthma, and had generally worse HRQoL than children with attention deficit hyperactivity disorder (ADHD) (152). In comparison to hypertension, diabetes and osteoarthritis, migraineurs scored lower in most domains, particularly those measuring wellbeing (mental health, emotional and social functioning) (112). Furthermore, migraineurs were also found to have higher comorbidity, especially with hypertension, irritable bowel syndrome, ulcers, and hearing and vision problems, compared to headache-free controls, which is a significant predictor of headache-related disability (147).

In summary, it is clear that much work has been devoted to assessing HRQoL in migraineurs within the headache field. These studies have demonstrated that migraine is associated with impairment in HRQoL, with reduced productivity and psychological comorbidity.

ii Tension-type headache (TTH)

The studies assessing HRQoL in TTH showed that, as expected, TTH was more prevalent compared to other headache disorders (130, 153-156), and patients with TTH had poorer HRQoL than healthy controls (153-155, 157). In episodic tension-type headache (ETTH), defined as having fewer than 15 TTH days per month, vitality and bodily pain scores of the SF-36 were significantly lower than controls (158), whereas in chronic tension-type headache (CTTH), with more than 15 TTH days per month, physical, social and role functioning were markedly impaired (3, 157). There was no significant difference in overall HRQoL between ETTH and CTTH patients, although work performance and physical health were more severely affected in the latter (159). Interestingly, patients with CTTH reported greater pain than episodic migraineurs, which may reflect headache chronicity rather than individual attack severity (3).

This goes in line with the finding that even though the majority of CTTH patients had a generalized impairment in functioning, which persists even outside of attacks (153), this was usually of moderate severity, without necessarily forcing cancellations of work or social commitments. Only a minority (up to 6%) rated their work performance as severely impaired and only 9% reported severe impairment in social functioning (157, 158). The greatest impairment was related to sleep, energy levels and emotional well-being (157). The degree of impairment in TTH is comparable to or greater than those with back problems or arthritis (157).

Holroyd and colleagues found that anxiety or mood disorders were three to 15 times as frequent in CTTH patients as controls (157). The observed depression was mild to moderate in severity, however anxiety was sufficiently high to impair functioning (157). The association between anxiety/depression and HRQoL in CTTH was investigated in one study, which suggested that anxiety has a mediating effect between headache frequency and vitality, social functioning and mental health, whilst depression had a modulatory effect on these same domains (160).

Although ETTH is the most prevalent headache disorder in the general population, most of the studies have focused on HRQoL in CTTH. This may be because the pain in ETTH is usually infrequent and mild, thus it is less likely to cause significant impairment. Even so, these studies indicate that TTH has a major impact on HRQoL, which is significantly worse relative to healthy controls, and also relative to episodic migraine sufferers on some HRQoL domains.

iii Cluster headache

The studies examining the impact of CH on HRQoL suggest that during active periods, CH patients have poorer HRQoL compared to the general population, with impairment being greater for patients with older age of onset of CH (161). This was most significant for the bodily pain, role physical, role emotional, general health, mental health, vitality and social functioning subscales of the SF-36 (4, 162). The higher pain score correlated with marked limitations in role and emotional functioning (4). Furthermore, CCH and active ECH patients were found to be more incapacitated compared to migraineurs (161), with significantly worse pain scores (3). Interestingly, ECH patients during a bout were found to have lower SF-36 scores compared to patients with previous myocardial infarction (4).

Comparing the different forms of CH, there was no significant difference in

impairment and HRQoL between ECH patients during a bout and CCH patients (161, 162). During the remission period of ECH patients, their HRQoL score tended to improve and became similar to headache-free groups (4). Conversely, Jurgens and colleagues found that disability remained high in ECH patients outside the bout, despite the absence of pain, which they speculate may have arisen due to the lack of a specified timeframe in the questionnaire used (The Henry Ford Disability Inventory) (161). Thus patients may have actually completed the questionnaire with their past bout in mind, rather than in their current headache-free condition. However, 13% of patients in another study also reported inhibition outside the cluster period, therefore raising the possibility that there is indeed a degree of impairment that extends beyond the cluster period, which could be attributed to unpredictability of the next bout, though further studies are required to confirm this (163).

Evaluation of the functional impact of this disorder using the HIT-6 questionnaire showed that 74% were severely impacted, whilst another study using a semi structured telephone interview found that 78% of CH patients reported restrictions in daily living and 96% reported having to make some form of lifestyle change (163, 164). Social and leisure activities, family life and housework were disrupted, with a high dependence placed on family and friends. In terms of paid work, 82% reported reduced ability to work, 16% lost their job and 8% had to retire early due to their headaches. Moreover, up to a third found that the disorder limited their career (161, 163). Taking into account this significant disability and the pain severity, it is therefore not surprising that agoraphobic and depressive symptoms, and suicidal tendencies are more prevalent in CCH (161, 164).

The excruciating pain coupled with night-time attacks affecting sleep and the agitation and restlessness during attacks are all assumed to have a major impact on HRQoL in

CH. Patients have reported that the impairment of their CH continues even outside of the cluster bout, with considerable impact on social and family life, having to frequently miss social events and family gatherings (163). Surprisingly however, the effect of CH on HRQoL is less marked, either when compared to headache-free controls or migraineurs, though this should be treated with caution, as the sample sizes of these studies were small (4, 161). Moreover, the lack of a specific CH HRQoL measure that can truly capture the inherent disabling and debilitating nature of this disorder may also account for the results seen.

iv Chronic daily headache

Chronic daily headache (CDH) is not a specific headache entity but is a term often used to describe any headaches that occur on 15 or more days per month, for at least three months. The most common types of CDH are chronic migraine (CM) and chronic tension-type headache (CTTH) (7).

The studies assessing HRQoL in CDH demonstrate that these patients have poorer HRQoL compared to the general population and patients suffering from severe episodic headache disorders (116-118, 146, 159, 165, 166). Mental health was markedly impaired, with reports of feeling irritated, fed up, frustrated and a tendency of giving up (166). Role physical, social functioning, role emotional, general health and vitality domains of the SF-36 in CM were significantly reduced compared to EM, with higher levels of depressive symptomatology exhibited (116). This impaired functioning correlates with the greater disability reported in CDH compared to their episodic counterpart, with reduced productivity at school and home (146, 159, 167). Headache frequency and comorbid depression has been found to have an independent and additive influence on HRQoL in CDH, with significantly reduced HRQoL in patients with CDH compared to those that suffer its episodic variant, suggesting that

chronicity of the headache may contribute greatly to HRQoL (117). To the best of my knowledge, HRQoL in hemicrania continua and new daily persistent headache has not been assessed.

1.3.d Predictors of HRQoL in primary headache disorders

Understanding the factors that influence HRQoL may enable us to manage and improve patients' symptoms and subsequently their HRQoL. Headache characteristics such as pain intensity (130, 134-136, 168-171), duration (144, 172) and (171, 172) frequency (107, 110, 117, 134, 144, 167, 171, 173) were found to be significant predictors of HRQoL. Likewise, presence of migrainous symptoms, particularly nausea, were also found to be important predictors in HRQoL (130, 134, 143, 149, 168), whereas combined photophobia and phonophobia are predictors of missed activity due to a headache (143). Greater headache-related disability was also a significant predictor of poor HRQoL, which was unsurprising as these concepts are inextricably linked (174). Comorbidity with other pain conditions negatively influences HRQoL (175, 176). Furthermore, the patients' psychological response to the pain experience and their coping mechanism has a great influence on HRQoL, and potentially may have a role in headache progression (134, 144, 149). Psychiatric comorbidity is associated with poorer HRQoL, with comorbid depression shown to have an independent and additive influence on headache-related disability (117). In CH, impairment worsened with increasing clinical severity and refractoriness of the headaches (161). However, it is important to note that even though all these factors can affect HRQoL, there is a marked individual impact, thus each patient will respond uniquely to these predicted factors.

1.3.e HRQoL across headache diagnoses

Primary headache disorders and their effect on one's ability to function in school, work or daily life in general, imposes a burden not only on the sufferers' themselves, but also on society, notably in terms of economic productivity and healthcare costs. Absenteeism and reduced work productivity, together with family and social restraints can lead to disruptions in occupational and personal domains, potentially creating a vicious cycle with worsening of headache, thus increasing its negative impact on HRQoL. Studies showed no significant differences in HRQoL between episodic migraine and TTH (119, 152, 155, 177), suggesting that the greater pain intensity of migraine is counterbalanced with the greater frequency of TTH (177). Although there is little variation in HRQoL between these headache groups, migraineurs report greater disability due to their headaches compared to TTH (106, 135, 171, 178-181) especially in work or school functioning (153). More missed days at school or work were reported by migraineurs, whereas reduced productivity at school or work were more prevalent amongst TTH patients (105, 167, 182, 183).

Solomon and colleagues found that patients with CH had significantly worse pain scores with limited social functioning compared to the other groups, although physical functioning was preserved. On the other hand, migraineurs had the least pain with greatest impairment in role functioning. Meanwhile patients with CTTH had reduced mental health scores with a generalized impairment in functioning (3). Furthermore, although HRQoL is lower in patients with CH compared to healthy controls, in comparison to migraineurs, their HRQoL is lower in two domains only; patients with ECH have shown significantly lower bodily pain and social functioning relative to migraineurs (4). Nonetheless CCH patients and ECH patients in a bout were found to be more disabled and incapacitated than migraineurs (161).

Primary headache disorders, irrespective of diagnosis, significantly diminishes HRQoL. Different types of headache affect different HRQoL domains. However, once it becomes chronic, the overall HRQoL significantly reduces. Furthermore, there is an increased prevalence of psychological comorbidity in headache disorders, which needs to be recognized and managed accordingly. These symptoms are likely to arise as a result of the pain and functional impairment associated with the headaches and the unknown fear of the next attack. Psychiatric comorbidity is associated with poorer HRQoL, with comorbid depression shown to have an independent and additive influence on headache-related disability (117). Thus, proper headache management requires attention not only to the headache pain itself, but also any associated comorbidity.

In terms of the instruments used, studies have show that there is moderate correlation ($r > 0.4$) between the generic and headache-specific HRQoL scales, indicating that there are measuring the same underlying construct i.e. HRQoL (184). The bodily pain and role physical domains of the SF-36 were most significantly affected in migraineurs, which correlated well with the impaired functioning seen, with more days of reduced productivity reported by these patients rather than days of actual missed activities (184). However, as previously mentioned, disease-specific HRQoL instruments have only been developed for migraine. CH has different headache characteristics compared to migraine and therefore specific instruments need to be developed to truly capture the impact of this disorder. In terms of number of studies done to date, there are only a handful of studies focusing on CH, which is considered to be one of the most painful conditions known to mankind, hence the need to explore this further.

1.4 Aim and objectives

From the discussion above, it is clear that CH is an excruciatingly painful and highly disabling disorder that warrants effective patient management. However, due to limited understanding of the pathophysiology involved, treatment is still largely empirically based. Most of the treatment arsenals used have sparse evidence and often are based on open label studies and consensus agreement. Thus, an insight into the treatment effects of the GONB, which is a commonly used efficacious transitional treatment in CH, may improve our knowledge in this field. In addition, a study of saccadic reaction times, which have been successfully used to improve understanding of other neurological disorders like Parkinson's and Huntington's disease, may be valuable in explaining the functional processes underlying CH. Finally, much work has been focused on assessing the HRQoL in migraine, with little attention devoted to CH. A number of disease-specific HRQoL scales have already been developed for migraine, whereas none are currently available for CH. Hence, this thesis attempts to address these gaps in knowledge by adopting a multifaceted approach, with the aim that it will broaden our understanding of this painful disorder.

1.4.a Aim

- To improve understanding of underlying mechanisms in CH and its impact on HRQoL.

1.4.b Objectives

- To perform functional magnetic resonance imaging (fMRI) to map and identify treatment effects of a GONB, by assessing changes in rCBF that relate to brain responses prior to and following a GONB. The main hypothesis of the

study was that the GONB would induce changes in the brain, as measured by rCBF, with specific changes postulated within the hypothalamus.

- To perform saccadometry to study saccadic reaction times, which may reveal meaningful insights into neural functioning in CH patients.

- To develop and validate a HRQoL measure specific for CH, which can be used within the clinical setting and in clinical trials as an objective patient-reported outcome measure.

- To assess the HRQoL of a large sample of CH sufferers, using a number of commonly used and validated HRQoL, disability and psychometric scales, specifically evaluating for differences between CH patients with episodic and chronic variants, with the hypothesis that patients with chronic CH will be more severely impacted by the disorder compared to their episodic counterparts.

Chapter 2 Functional neuroimaging study

2.1 Introduction

CH is an excruciatingly painful disorder, thus it is crucial that patients are well managed from the onset. As previously discussed in Chapter 1, currently there are both medical and surgical interventions available for these patients. However, because of our limited understanding of the pathophysiological basis of the disorder, treatments are largely empirical based (2). Hence, although there are a number of treatments available, some patients can still be poorly managed and be difficult to treat.

To recap from the previous chapter, the medical treatment available includes acute, preventive and transitional therapies, whereby the latter allows a short-term solution in controlling the CH attacks. This includes the use of a GONB, which has been shown to provide pain relief in CH (55, 56). Several studies have demonstrated that this procedure is highly effective, rendering at least half of CH patients pain-free for up to four weeks. Furthermore, it has been shown to have a minimal side effect profile (53, 56, 62, 63, 65). These positive findings support the use of GONBs in clinical practice and thus it has been widely used as a standard form of treatment in patients with CH, as part of their headache management plan.

However, the mechanism of action of this intervention is poorly understood. There have been speculations that its mode of action is centred at the level of the trigeminal nucleus caudalis, where the cervical and trigeminal systems converge, with the GONB reducing cervical afferent input to the nucleus and possibly interrupting the trigeminal autonomic reflex pathway (53, 56-58).

Due to this gap in knowledge, the effect of a GONB on brain function in CH patients was explored using a perfusion magnetic resonance imaging technique, specifically arterial spin labeling, with the aim of developing a better understanding of the mechanisms by which this transitional therapy exerts its therapeutic effect. In particular, the GONB was hypothesized to induce changes in brain function, as measured by changes in rCBF. Due to a priori knowledge of the possible pivotal role of the hypothalamus in CH pathophysiology, the changes in rCBF were thus hypothesized to specifically include this region.

2.1.a Perfusion magnetic resonance imaging

Perfusion imaging is a functional neuroimaging modality that allows measurements of cerebral perfusion, which is the rate of change of blood flow per unit of cerebral tissue per unit of time (ml/100g/min). Although electrophysiological studies, such as microelectrode recordings, allows a direct measure of brain function, the invasive nature of the technique limits it use in human research. Other methods such as electroencephalography (EEG) and optical imaging techniques also have their limitations in terms of poor spatial resolution and risk of toxicity (185, 186). Hence, whilst functional neuroimaging provides an indirect measure of neural function, the close coupling between cerebral perfusion and metabolism, or neural activity, means that measurements of the former is a sensitive indicator of regional brain function (187) The fundamental basis for functional neuroimaging lies within the complex interaction between increased metabolic requirements during neuronal activity and the supply of this energy indirectly via the vascular system, in the form of oxygen and glucose, through an increased blood flow to the required site (186). A previous study combining intracortical measurements of brain activity and functional imaging in monkeys have provided evidence of the tight link between

this haemodynamic response and neural activity (185). Moreover, it has also demonstrated that the response may be related to the incoming neural input and intracortical processing, rather than its output or spiking activity, thus shedding light on the aspect of neuronal excitation that is being measured (185).

Studies of brain function are invaluable in advancing our understanding of the human brain in healthy and diseased states. Several perfusion imaging techniques are available, with positron emission tomography (PET) scanning being one of the earliest available modality (187, 188). However, drawbacks of this technique include the need to use an exogenous radioactive tracer and exposure to ionising radiation, thus limiting its use in studies investigating treatment effects that require repeated assessments. Moreover, PET scanning is costly and suffers from relatively poor temporal resolution (188).

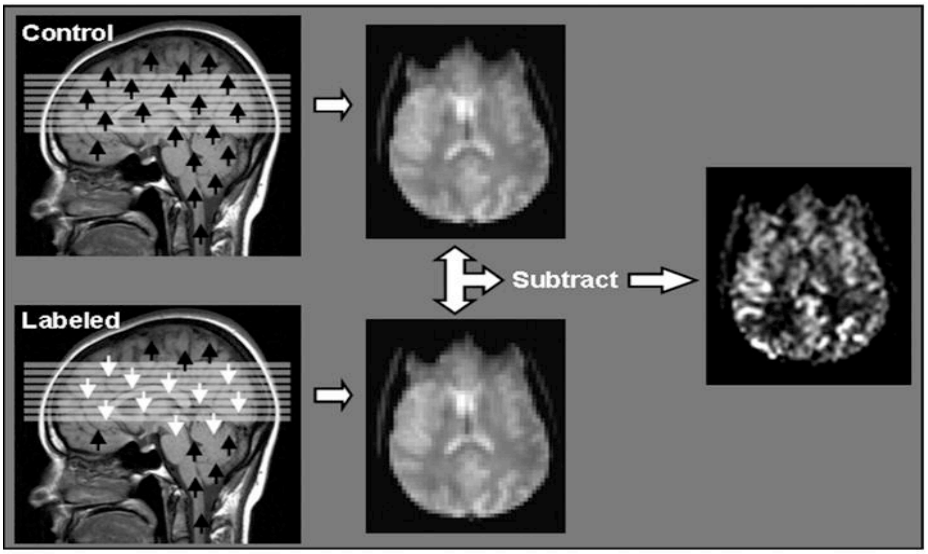
An alternative perfusion imaging modality is functional magnetic resonance imaging (fMRI), which has gained popularity due to its lower cost, non-invasive nature, lack of exposure to ionising radiation and superior temporal and spatial resolution (189). Blood oxygen level dependent (BOLD) fMRI is the most commonly used technique, with haemoglobin being used as an endogenous tracer (190). This technique relies on changes in cerebral blood flow (CBF) and oxygen consumption as a marker of neuronal activity, with the functional contrast derived from changes in relative quantities of oxygenated and deoxygenated haemoglobin, which have different magnetic properties (190, 191). Despite its excellent sensitivity to functional stimulation, the BOLD signal is unstable over time and thus is best suited for measuring CBF changes over the course of several seconds only (188). Moreover, it only provides a relative, rather than an absolute measure of CBF and lacks an absolute baseline measure, thus reducing the interpretability of

data across scanning sessions (188, 190-192). Hence, traditional 'evoked-response' BOLD fMRI has significant limitations for use in studies measuring treatment effects. An alternative approach is arterial spin labelling.

2.1.b Arterial spin labelling

Arterial spin labelling (ASL) is an fMRI technique that allows a quantitative and reproducible measurement of regional cerebral blood flow (rCBF) throughout the brain and is ideal for investigating ongoing pain states (193-198). A recent test-retest reliability study has shown that it has good potential for comparing within- and between-subject differences in ongoing pain (194). Arterial blood water is utilised as an endogenous tracer, which is magnetically labelled by application of radiofrequency pulses prior to the tissue of interest, as shown in Figure 2.1. This process, known as inversion, alters the magnetisation of the protons within arterial blood water, such that it differs from the static tissue magnetisation (187, 188). The inflowing labelled protons, which acts as a diffusible tracer, passes into the cerebral tissue and exchanges with the unlabelled protons in cerebral tissue water, thus changing the tissue magnetisation in that region, with change being proportional to cerebral perfusion (188, 199). An MRI image is then acquired, which is referred to as the tagged image. A control image of the region is subsequently acquired without labelling of arterial blood water, and a measure of rCBF in units of ml/g/min at each voxel obtained by pairwise subtraction of the control image from the tagged image (187).

Figure 2-1 Diagram of arterial spin labeling. Arterial blood water is magnetically labelled (white arrows) by applying radiofrequency pulses prior to the tissue of interest. These inverted spins acts as a diffusible tracer, which exchanges with the unlabelled protons in cerebral tissue water and changes tissue magnetisation in that region. An MRI image is acquired, referred to as the tagged or labelled image. A control image of the region is subsequently acquired without labelling of arterial blood water, and a measure of rCBF in units of ml/g/min at each voxel obtained by pairwise subtraction of the control image from the tagged image. Reprinted from Wolf and Detre (200).



i Comparison of ASL to other perfusion imaging modalities

Studies comparing rCBF measurements between ASL and ^{15}O-PET within the same subjects, both at rest and with functional stimulation have shown excellent correlation between the two modalities (187, 188). Meanwhile in comparison to BOLD fMRI, ASL generally suffers from low signal-to-noise ratio (SNR) and thus is less sensitive (187, 188, 192). As a result, thicker image slices are often acquired and scanning performed in higher magnetic field strengths to improve sensitivity (188, 189). Additionally, due to the time delay (between 4 – 6 seconds) between

acquisition of the tagged and control images, ASL also suffers from lower temporal resolution (187, 188, 190). However, spatial resolution of ASL fMRI may be relatively superior to BOLD fMRI, owing to the rapid decay time of its tracer (arterial blood water), which is approximately 1 second, thus limiting its accumulation in venous structures. Consequently, there is better localisation of signal changes over activated cortex (188, 189). Moreover, since tagged and control images are usually acquired in an interleaved manner, motion artefacts and baseline drift are reduced in ASL, thus offering better temporal stability (188, 189).

ii Methods for labelling

Several methods are available for labelling of arterial blood water, which can be grouped into continuous ASL (CASL) and pulsed ASL (PASL) techniques. As the name suggests, in CASL, there is a continuous inversion of arterial blood water as it flows through a specified plane, commonly using flow driven adiabatic inversion, with a constant radiofrequency pulse (187). Meanwhile, in PASL, a volume of arterial blood water is inverted instantaneously proximal to the tissue of interest (187, 188). Even though there is a greater perfusion contrast and higher signal-to-noise ratio (SNR) with CASL compared to PASL technique, technical restraints associated with application of a constant radiofrequency pulse is a limiting factor (188, 201). Furthermore, possible deposition of significant radiofrequency power to subjects from the use of a constant pulse can be limiting at high magnetic field strengths (188). Therefore, pseudocontinuous labelling paradigms have been developed for CASL to overcome these limitations, termed pulsed continuous arterial spin labelling (pCASL), which was utilised in this study.

2.2 Methods

2.2.a Subjects

Fifteen patients seen at the headache clinic at The National Hospital for Neurology and Neurosurgery, Queen Square, with a diagnosis of CH, according to the ICHD-II diagnostic criteria, and were receiving their first GONB as part of their headache management plan were recruited in the study (7). Two patients failed to attend their follow up scan, and therefore their data were not included in the final analysis. Patients were instructed to abstain from alcohol for 24 hours and from caffeine-containing products for 12 hours prior to each scanning session. In addition, they were asked to abstain from the use of tobacco- or nicotine-containing products for 4 hours prior to admission until discharge for each session. Ethical approval for the study was obtained from the National Research Ethics Service London-Queen Square Research Ethics Committee (reference: 12/LO/0419). Written informed consent for study participation was obtained from all subjects prior to the study.

2.2.b Inclusion and exclusion criteria

Subjects had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

- Male subjects diagnosed with CH in accordance with the ICHD-II diagnostic criteria. This study is limited to male participants only, as CH is more common in males than females (male to female ratio 2.5-7.2:1), and also to exclude any possible influence of the female hormone cycle on pain perception and response (1, 202).

- Aged between 18 and 65 years inclusive.

- Receiving their first GONB as part of their headache management plan.
- Body Mass Index (BMI) of approximately 18 to 30 kg/m^2; and a total body weight 50-100 kg, due to the weight limit and restrictions of the scanner used.
- Able to lie still within the environment of the MRI scanner for the required period to perform the study, with no contraindications to MRI scanning (e.g. metal, pacemaker, etc).
- Should be on a stable dose of preventive medications for at least a month, if on preventives.
- Has not used an abortive treatment within the last 12 hours prior to the study. The use of oxygen as an abortive was permitted up to 1 hour prior to the scan.
- No history of psychosis or psychological disease.
- No evidence of a history or current use of drugs of abuse.
- Does not consume more than six cups of caffeinated drinks per day.
- No existing medical problems, for example, uncontrolled hypertension, renal failure, cancer, liver disease, severe spinal trauma, active thyroid disease, congestive heart failure, etc.

2.2.c Psychometric measures

A range of psychometric and pain disability measures were utilised, providing measures of personality, trait and state anxiety, depression, and coping strategies for pain.

The McGill Pain Questionnaire (MPQ) provides quantitative information of a patient's subjective pain experience that can then be treated statistically. It gives a multidimensional reflection of how patients perceive their pain, allowing measurements of the sensory, affective and evaluative aspects of pain (203, 204).

A number of different emotions are incorporated within the emotional aspect of pain. However, they are primarily negative, with anxiety and depression being the most common. It has been reported that up to 50% of patients with chronic pain suffer from depression, and within the primary care setting, almost one third of headache sufferers have symptoms of depression (205, 206). The Hospital Anxiety and Depression Scale (HADS) is an instrument that has been widely used in the clinical setting to screen for the separate symptoms of anxiety and depression. It consists of a seven-item depression score alternating with seven items that assesses anxiety, and has been found to be comparable to other comprehensive measures of anxiety disorders and depression (207).

Cognitive and behavioural responses to pain form important determinants of the pain experience, with higher catastrophising being associated with greater headache pain (208). An assessment of coping strategies was conducted using the Cognitive Coping Strategies Inventory Revised scale (CCSI-R). This consists of six subscales of items measuring different specific coping strategies and a seventh subscale to assess catastrophising (209).

The patients' quality of life was assessed using the SF-36, which is a self-administered, 36-item health-related questionnaire measuring functions in eight domains. This includes physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health (210).

An assessment of the patients' personality was made using the short form of the revised version of the Eysenck Personality Questionnaire (EPQ-R). This is a 48-item questionnaire that evaluates three dimensions of personality, namely extraversion-introversion, neuroticism-stability and psychoticism-socialisation (211). This instrument has been widely used and is one of the best validated instruments in the personality literature (212).

The emotional and functional impact of the patients' headaches on daily living was assessed using the Henry Ford Disability Inventory (HDI). This is a 25-item questionnaire, which can be repeated periodically to give a measure of effectiveness of management strategy over time.

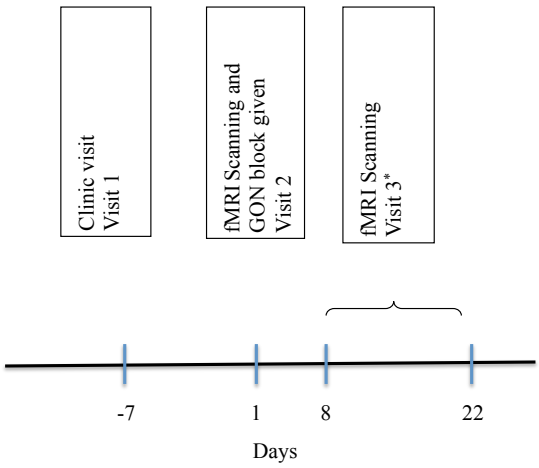
The adverse impact of the patients' headaches will be made using the six-item Headache Impact Test (HIT-6). This evaluates six aspects namely the adverse impact of their headaches on social, role and cognitive functioning, vitality, psychological distress as well as providing a measure of the severity of their pain (213). This tool was developed for use in both clinical research and practice, to allow monitoring of patients with headaches. Patients attending the headache clinic at The National Hospital for Neurology and Neurosurgery are routinely required to fill this questionnaire during each clinical visit as part of their pain disability measure.

2.2.d Study design

The study was a prospective, open-label design, comprising of two scanning sessions, with each visit involving a stay of approximately two hours at the study site. The first session served as baseline scans; to map the cerebral representation of the interictal state of CH patients, whilst the second session were follow-up scans following response to the GONB. A comparison across these sessions should determine the effects of treatment on brain function of CH patients. The timeline for the scanning sessions is shown in Figure 2.2.

The scanning sessions were performed at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London. Patients' pulse rate and blood pressure were recorded at each session. Prior to the start of each scanning session, all patients had to provide a urine sample to screen for any abnormalities on standard urinalysis test and for evidence of use of drugs of abuse, and also underwent an alcohol breathalyser test.

Figure 2-2 Timeline for scanning sessions
fMRI = functional magnetic resonance imaging, GON = greater occipital nerve, GONB = greater occipital nerve block



*Visit 3 scheduled within 7-21 days after GONB given

i Scanning session 1

Patients initially underwent a mock scanning session in a dummy scanner to allow them to become accustomed to the MRI environment, whilst also simultaneously being trained to operate the hand-held joystick, which was used during the scanning session to rate their pain and alertness level on a computerised VAS. A complete psychometric analysis was also performed and patients given a daily headache diary for them to record the frequency, duration and intensity of their headaches. They were expected to continue recording their headaches until the day of their follow up scanning session. Patients then underwent a series of scans, including an initial localiser scan to register their head to the scanner, T2 structural

scans for image registration and four consecutive CASL scan examinations, with each CASL lasting approximately six minutes.

ii Scanning session 2

To allow for response to the GONB, this visit was scheduled at approximately 7-21 days following the injection, although there was some flexibility according to treatment response. The headache diary was collected from all patients during this visit, as well as pain and headache disability measures and anxiety/depression scores. During this session, patients again underwent a series of scans, including an initial localiser scan to register their head to the scanner, T2 structural scans and four consecutive CASL scan examinations.

2.2.e Image acquisition

Qualified radiographers conducted all image acquisitions using a 3T General Electric Signa HDX whole-body MRI scanner, fitted with an 8 channel, receive-only, phased-array head coil. Following an initial localizer scan to register patients' head to the scanner, high-resolution T1- and T2-weighted images were acquired for image registration. Whole-brain resting perfusion measurements were made with a pulsed continuous arterial spin labelling (pCASL) sequence, which was labeled using a train of Hanning radiofrequency (RF) pulses of 500 μs duration, 1500 μs pulse gap and 1.5 seconds total labeling duration. Each imaging session did not exceed 60 minutes and patients were instructed to lie still with their eyes open.

Quantification of whole brain resting state rCBF using CASL was repeated four times within a session for determination of the temporal, short-term variation of rCBF. Visual analogue scale estimates of perceived pain intensity and alertness were acquired using a computerized scale. The VAS was controlled by the user

using a hand-held joystick to alter the position of a 'needle' on a screen in front of them. The scale has a data range of 0-100, anchored at 0 (no pain/very sleepy) and 100 (worst pain imaginable/wide awake). VAS responses of perceived pain preceded and followed each CASL acquisition.

2.2.f Data analysis

i Clinical characteristic, headache diary and psychometric data analysis

Clinical characteristics and headache diary data as well as scores from the psychometric and quality of life questionnaires were entered into and analyzed using SPSS version 21. Clinical characteristics, headache diary data and scores from the SF-36 Health Survey, CCSI-R, EPQ-R, MPQ, HIT-6, HDI and HAD scales were described using descriptive statistics.

ii fMRI data analysis

The sample size calculation for this study was powered on a recent neuroimaging research study using the third molar surgery model (195). All preprocessing and data analyses were conducted using perfusion analysis toolboxes available in FSL suite version 4.1.8 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk). Pre-processing procedures were applied to the images acquired prior to any analysis to remove unwanted variability from the data, such as any artifacts or noise, to allow for motion correction, to correct for anatomical variations between patients and standardize the images to allow for between-subject comparisons, and in doing so, prepares the data for statistical analysis (186).

a Pre-processing of images

The BET, FLIRT, FNIRT and SUSAN command tools were used to preprocess the images. The steps involved included skull stripping, registration, normalization and smoothing.

Registration is the spatial alignment of two or more image volumes, and relies on an image similarity measure between pairs of voxels in the same position (186). This step is essential to ensure that each voxel represents the same region of the brain within patients, as any amount of movement within the scanner can potentially cause changes in voxel intensity, which can subsequently be misinterpreted as signal activations. Thus, rigid body transformation was used for correction of head movements within patients. This assumes that the size and shape of their heads remain constant, and that head movement can only occur either by translation or rotation (186). However, taking into account variations in brain sizes and shapes between patients, images have to be transformed into a standard reference space to allow for comparisons across patients. This is known as spatial normalization and consists of both linear and non-linear transformations. The Montreal Neurological Institute (MNI) brain was utilized as the standard brain template in this study.

Prior to registration, the T2 structural scan was skull stripped to extract brain tissue from the acquired images and a mask created. The skull stripped T2 structural image was then normalized into standard MNI space. Each of the four CASL scans acquired per patient in each session were initially realigned to the first scan to correct for the small amounts of movement, and then coregistered to the skull stripped T2 structural image. Coregistration overcomes the low-resolution

limitations of functional images by allowing an overlap between the structural and functional data, so that any areas of activation can be correctly correlated to their anatomical position (186). A matrix was then created and the T2 skull stripped mask used to extract brain from the CASL scans and normalize them into standard MNI space. Finally, the images were spatially smoothed using the SUSAN command tool, which applies a non-linear filtering algorithm, averaging voxels to nearby voxels with similar intensity, to accommodate for structural variability across patients and to improve the normality and the SNR of data (186).

b First level analysis

In the first level analysis, the four CASL series for each patient in each session that have undergone preprocessing were merged to create a 4D image and a grey matter mask, derived from the probabilistic MNI grey matter template was applied. This removes white matter voxels from the image, and voxels with a greater than 20% likelihood of being grey matter were included in the mask. The merged four CASL series was then averaged using the FLAME (FMRIB's Local Analysis of Mixed Effects) tool, and a mean image with its calculated variance was generated for the second level analysis.

c Second level analysis

Individual patient data from first level analyses provided inputs to second level analysis to allow comparisons across patients, in order to determine the treatment effects of the GONB in the brain by detecting changes in rCBF before and after treatment. A higher-level mixed effects general linear model (GLM) analysis was computed using the FLAME tool. The GLM, at each voxel in the image, models

the observed fMRI signal as the sum of the effects of a series of predictor variables plus residual random error, and can be expressed by the following equation:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_{2 + \ldots . +} \beta_n X_{n +} \varepsilon$$

where Y = observed fMRI data (dependent variable)

β_0 = a constant, reflecting the baseline signal intensity

β = variable weight (parameter estimate)

X = predictor variable (independent variable)

ε = residual error

The GLM analysis used a paired t-test design at each voxel (univariate analysis), to determine if there is a significant relationship between the predictor variables (design matrix) and the observed fMRI signal (186). Patients and scanning sessions (pre-GONB and post-GONB) were defined as the predictor variables to assess changes in rCBF following the GONB. Global blood flow effects were accounted for by mean centering the global blood flow measurements across subjects, which was then added to the model as a covariate (predictor variable) to reduce the amount of error and thus increase the statistical power to detect changes in rCBF between pre- and post- GONBs (Figure 2.3).

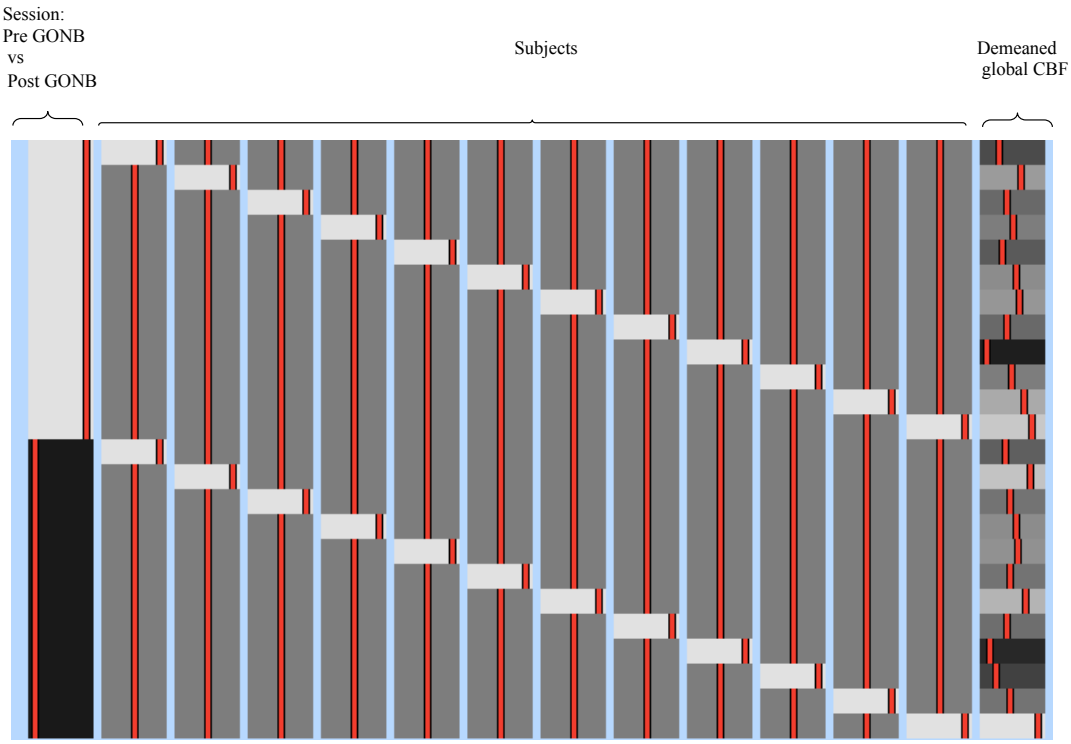
Since fMRI data contains thousands of voxels, multiple comparisons testing of each voxel is likely to yield a high number of false positive results. Thus to overcome this, multiple comparison correction measures must be applied. Bonferroni correction takes into account the number of independent statistical tests (voxels). Considering that nearby voxels are highly correlated and therefore are not

truly independent, the number of independent statistical tests will be overestimated and Bonferroni correction will be much too conservative. Alternatively, Gaussian random field theory provides a better estimate of independent tests based on the spatial resolution of the data (186). After appropriate statistical thresholding ($Z > 2.3$ and cluster-corrected alpha < 0.05), resulting statistical parametric maps were generated and anatomical brain/brainstem atlases were used to identify the anatomical locations of the observed clusters (214, 215). Post-thresholding, the brain regions with voxels that have the highest Z-score (peak Z-scores) within the observed clusters were identified using mri3dX software (version 7.79). The anatomical locations of these clusters were identified using the Talairach Daemon software in mri3dX and Duvernoy's brain and brainstem atlases (214, 215).

d Region of interest analysis

Based on previous neuroimaging findings of hypothalamic activation in CH patients, which is speculated to have a pivotal role in the pathophysiology of the disorder, a region of interest (ROI) was created for the hypothalamus using Duvernoy's brain and brainstem atlases (214-216). The hypothalamus was hypothesized to show reductions in rCBF following a response to the GONB.

Figure 2-3 Second level analysis design matrix. Matrix corresponds to the experimental design, with columns for each predictor variable. The column on the far left illustrates the two scanning session i.e. pre-GONB (top half of matrix) and post-GONB (bottom half of matrix), followed by one column each per patient, to assess changes in rCBF following the GONB. Demeaned global CBF was added to the model as a covariate (column far right).



CBF = cerebral blood flow, GONB = greater occipital nerve block

2.3 Results

2.3.a Subjects

Following preprocessing, data from one patient had to be excluded due to presence of artifacts from head movement that could not be corrected for, thus only data from 12 patients were included in the final analysis. Data from these patients are presented in Table 2.1. The patients had a mean age of 39.8 ± 9.8 years (range 29 – 64 years). Eight patients (66.7%) had ECH whilst four (33.3%) had the chronic variant. Nine

patients (75.0%) had strictly left-sided headaches, two (16.7%) had strictly right-sided headaches and one patient (8.3%) had unilateral side-variable headaches, with more frequent attacks on the left. Five patients had a complete response to the GONB and were rendered pain-free for at least a week; four had a partial response, with improvement in headache symptoms (either frequency, duration or intensity) by ≥ 30%, whilst three patients had no benefit from the GONB. The mean number of days between the two scanning sessions was 13.8 days (range 6 – 25 days).

Table 2-1 Clinical characteristics of patients

Patient number	Age (years)	Side of CH	Type of CH	Disease duration (years)	Response to GONB
1	39	L	ECH	16	P
2	29	L	ECH	9	P
3	37	R	CCH	24	N
4	46	L	ECH	4	C
5	34	R	ECH	18	C
6	50	L	CCH	8	C
7	64	L	ECH	43	C
8	35	L	ECH	8	P
9	32	L+R	CCH	11	N
10	34	L	ECH	12	P
11	34	L	CCH	7	N
12	43	L	ECH	27	C
Mean ± SD	39.8 ± 9.8			15.6 ± 11.1	

CH = cluster headache, ECH = episodic cluster headache, CCH = chronic cluster headache, GONB = greater occipital nerve block, L = left, R = right, C = complete response, N = no response, P = partial response, SD = standard deviation

2.3.b Headache diary data

The headache characteristics at baseline and following the GONB are shown in Table 2.2 and illustrated as box plots in Figure 2.4. There were trends for improvement in headache frequency, duration and severity after the GONB, with reduction in median

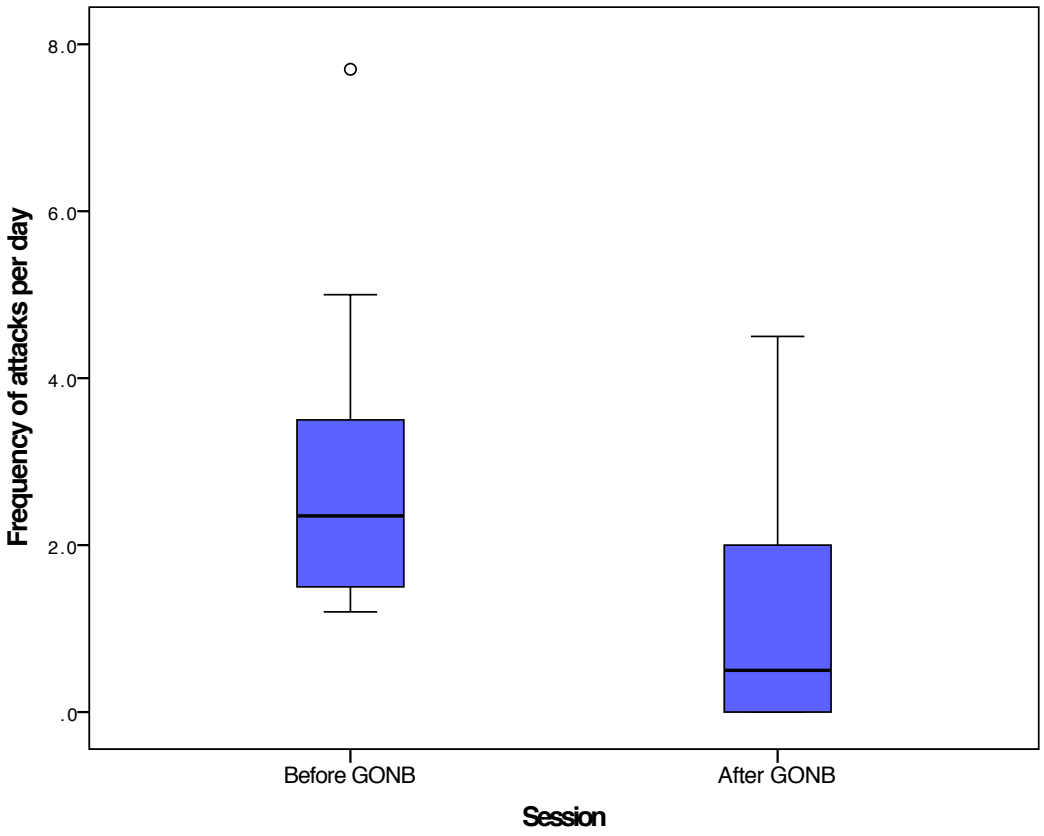
frequency of headaches from 2.4 attacks per day to 0.5 attacks daily. Median duration of attacks were reduced from 49.2 minutes at baseline to nil after treatment, and median severity of CH attacks reduced from visual rating scale (VRS) 7.9 (denoting severe pain) at baseline to 1.0 (denoting mild pain) after the GONB.

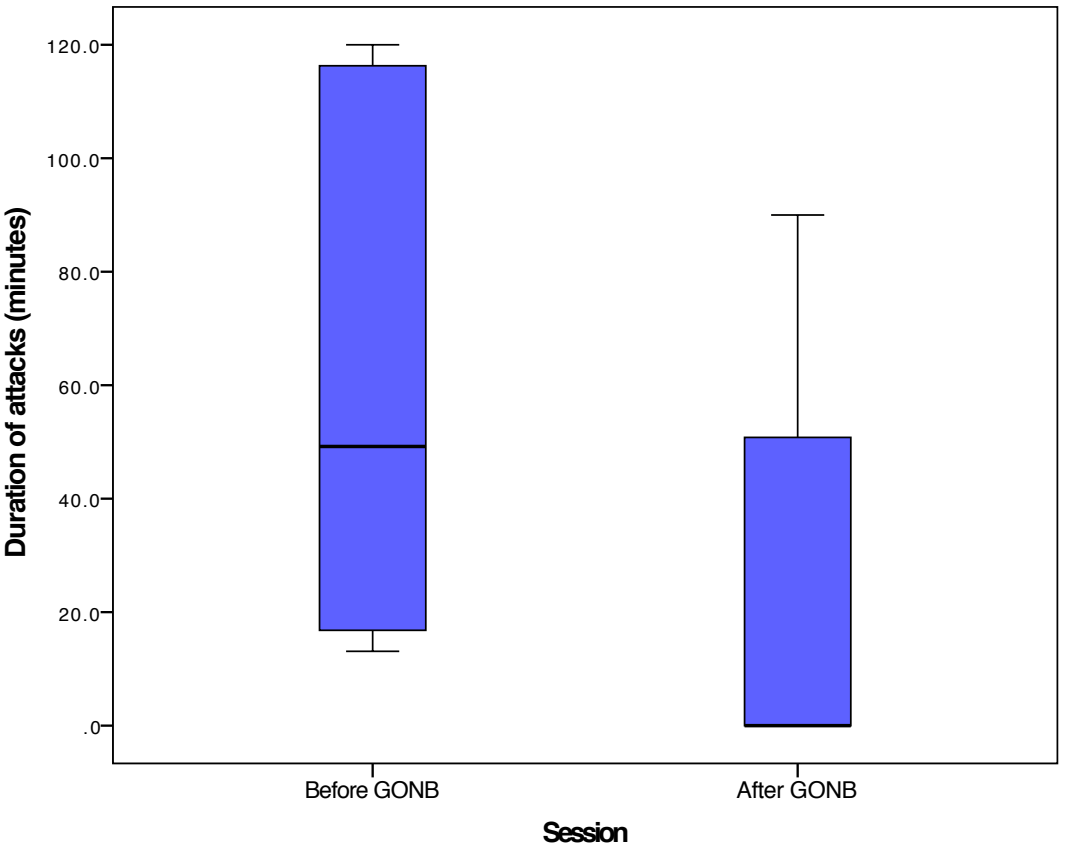
Table 2-2 Headache characteristics at baseline and following the GONB

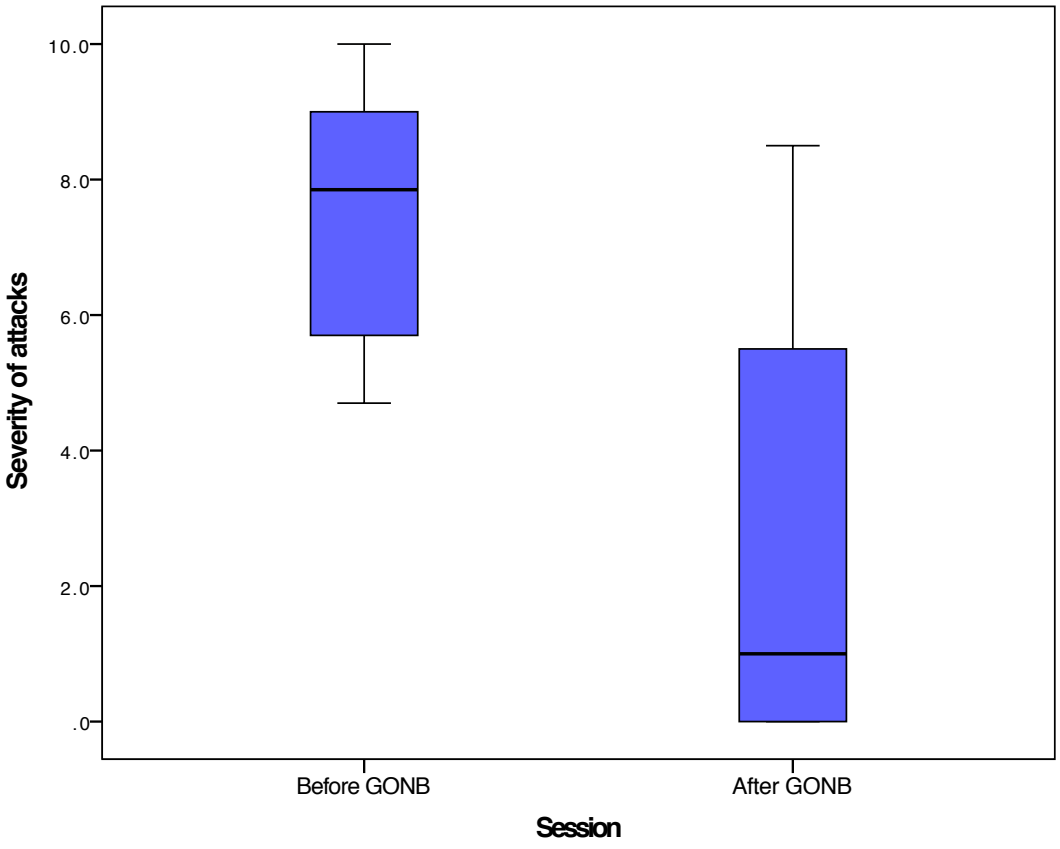
Headache characteristic	Pre-GONB	Post-GONB
Frequency per day		
Mean ± SD	3.0 ± 2.0	1.2 ± 1.6
95% confidence interval	1.5 – 4.5	0.1 – 2.3
Median (range)	2.4 (1.2 – 7.7)	0.5 (0 – 4.5)
Duration (minutes)	61.6 ± 45.5	27.3 ± 38.6
Mean ± SD		
95% confidence interval	22.0 – 88.1	-2.4 – 57.0
Median (range)	49.2 (13.1 – 120)	0 (0 – 90)
Severity (VRS)	7.6 ± 1.8	2.5 ± 3.1
Mean ± SD		
95% confidence interval	6.0 – 8.7	-0.2 – 4.5
Median (range)	7.9 (4.7 – 10)	1.0 (0 – 8.5)

GONB = greater occipital nerve block, VRS = visual rating scale, SD = standard deviation

Figure 2-4 Box plots illustrating the frequency, duration and severity of CH attacks before and after the GONB. Dark horizontal lines represent the median, with the box representing the upper and lower quartiles, the whiskers the minimum and maximum values, and outliers represented by dots.
CH = cluster headache, GONB = greater occipital nerve block




120.0
100.0
80.0
60.0
40.0
20.0
.0
Duration of attacks (minutes)
Before GONB
After GONB
Session


10.0
8.0
6.0
4.0
2.0
.0
Severity of attacks
Before GONB
After GONB
Session

2.3.c Psychometric and quality of life data

The mean scores from the psychometric and quality of life measures used in this study are shown in Table 2.3. Patients had moderate scores on all the three subscales of the CCSI-R scale and the EPQ-R scale. Patients scored lowest for role physical, role emotional and bodily pain domains of the SF-36 Health Survey, reflecting the high degree of pain and functional impact associated with their headaches. This corresponds to the high disability scores on the HDI, mean ± SD (68.2 ± 25.6) and HIT-6 scales (63.8 ± 4.2), with a trend for improvement seen on the HDI scale following the GONB (49.5 ± 30.6) (Figure 2.5). In terms of patient-reported measures of anxiety and depression, which was measured by the HADS, patients had borderline symptoms (mean score ≥ 8) prior to the GONB, with a trend for improvement after treatment, as shown in Figure 2.6.

Table 2-3 Mean scores from the psychometric and quality of life measures

Scale	Mean score ± SD pre GONB	Mean score ± SD post GONB
CCSI_R		
Distraction	2.1 ± 0.6	
Catastrophising	2.8 ± 0.7	
Coping	2.8 ± 0.5	
EPQ-R		
Psychoticism	6.7 ± 2.9	
Neuroticism	12.2 ± 4.2	
Extraversion	10.6 ± 5.2	
Lie	12.0 ± 2.8	
SF-36 Health Survey		
Physical functioning	78.8 ± 20.5	
Role physical	6.3 ± 11.3	
Bodily pain	22.4 ± 22.3	
General health	61.4 ± 22.2	
Vitality	36.3 ± 18.7	
Social functioning	41.7 ± 30.3	
Role emotional	36.1 ± 43.7	
Mental health	53.0 ± 25.7	
HDI total	68.2 ± 25.6	49.5 ± 30.6
HIT-6	63.8 ± 4.2	61.2 ± 6.6
MPQ total	21.5 ± 14.0	12.1 ± 11.5
MPQ VAS	5.9 ± 3.9	2.9 ± 3.1
HADS		
Anxiety	8.4 ± 5.4	7.9 ± 4.3
Depression	8.7 ± 5.4	7.1 ± 4.3

SD = standard deviation, GONB = greater occipital nerve block, CCSI-R = Cognitive Coping Strategy Inventory-Revised, EPQ-R = Eysenck Personality Questionnaire-Revised, SF-36 = Short-Form-36, HADS = Hospital Anxiety and Depression Scale, HDI = Henry Ford Headache Disability Inventory, HIT-6 = Headache Impact Test, MPQ = McGill Pain Questionnaire, VAS = visual analogue scale

Figure 2-5 Box plot showing improvement in mean HDI total score following the GONB. Dark horizontal lines represent the median, with the box representing the upper and lower quartiles, the whiskers the minimum and maximum values.
HDI = The Henry-Ford Headache Disability Inventory, GONB = greater occipital nerve block

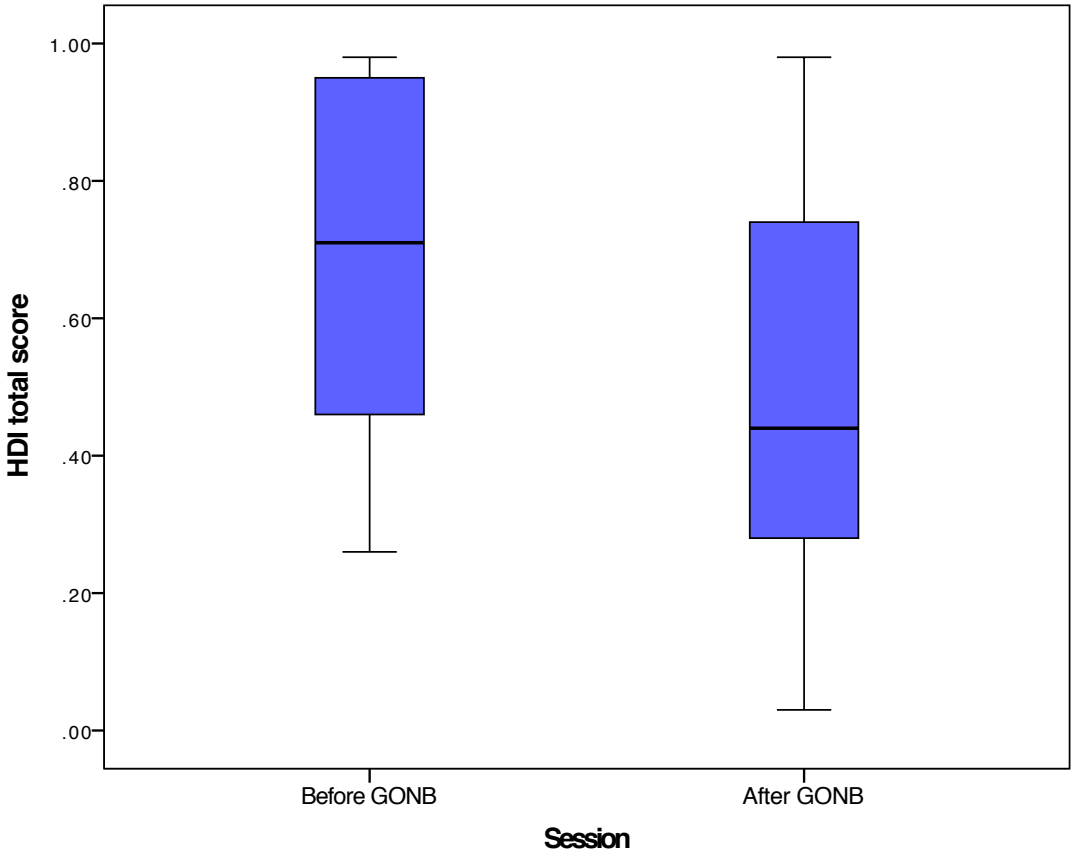
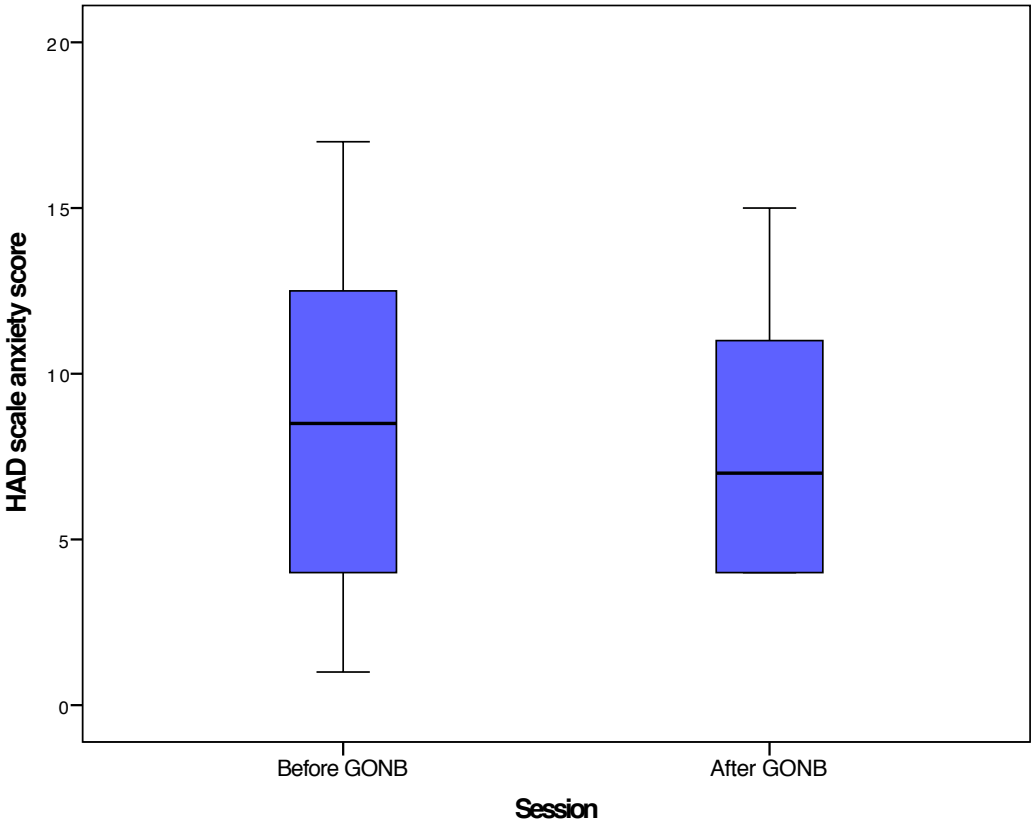
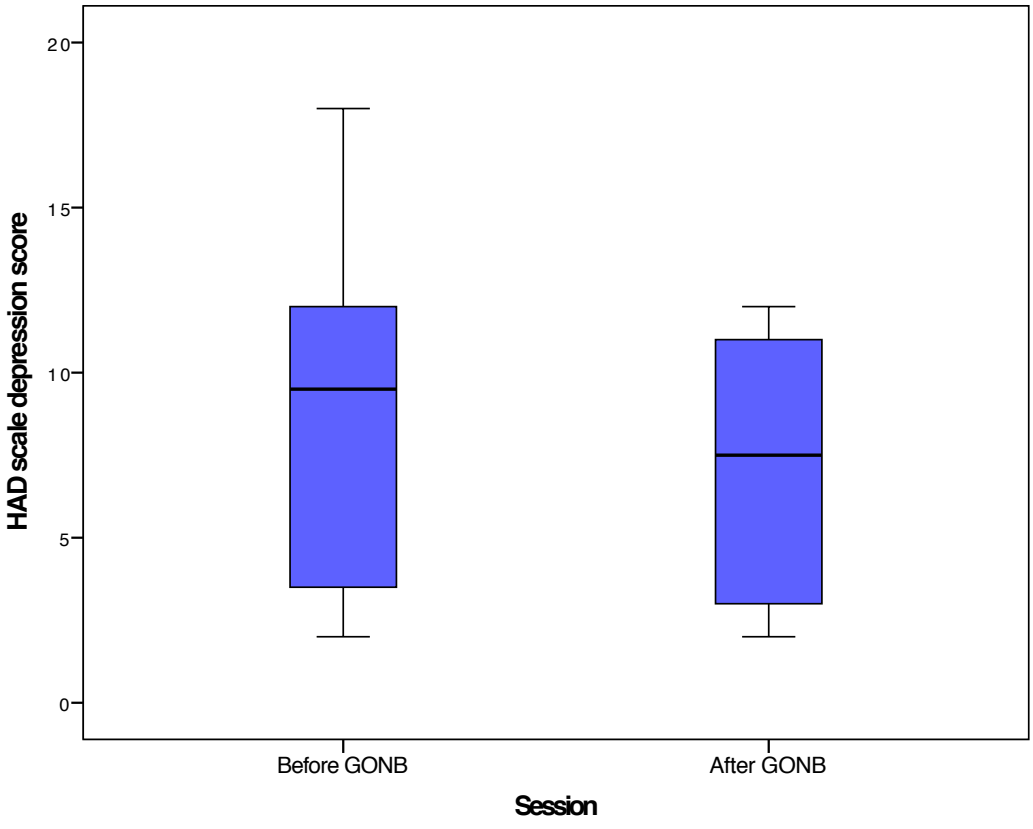


Figure 2-6 Box plots showing anxiety and depression scores before and after the GONB. Dark horizontal lines represent the median, with the box representing the upper and lower quartiles, the whiskers the minimum and maximum values. GONB = greater occipital nerve block, HAD = Hospital Anxiety and Depression

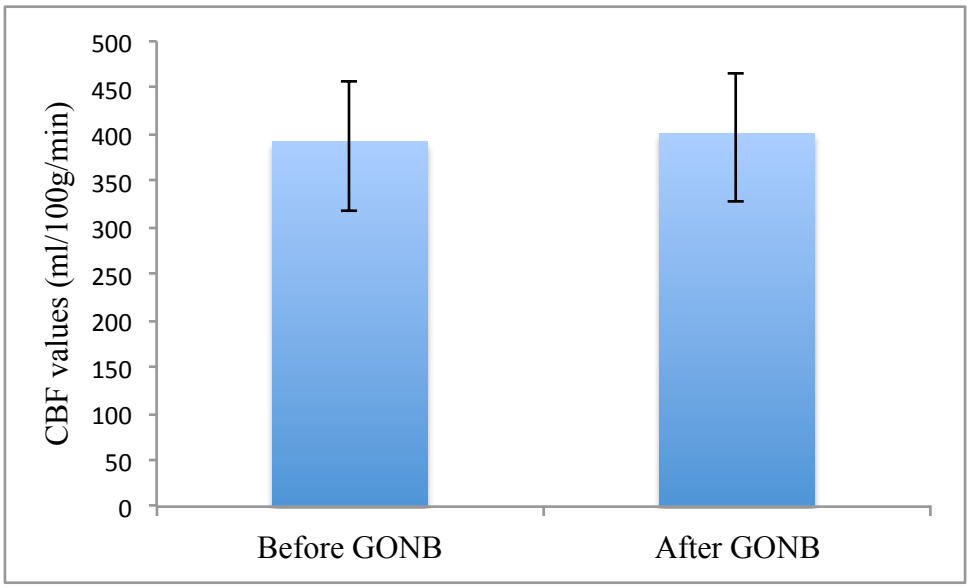




2.3.d Neuroimaging data

Global blood flow was measured and averaged across patients in each scanning session. A comparison of mean global blood flow before and after the GONB demonstrated that there were no significant differences between the scanning sessions; $t(11) = -0.65$, $p = 0.53$ (Figure 2.7). Therefore, since global CBF was not affected by treatment, it was justifiable to add it as a covariate in the design matrix.

Figure 2-7 Bar chart comparing mean global CBF before and after the GONB. Error bars represents standard deviation. CBF = cerebral blood flow, GONB = greater occipital nerve block



There were two distinct clusters of brain region that showed significant increases in rCBF in CH patients prior to having their GONB, in particular, within the left basal ganglia and the brainstem bilaterally, as shown in Figure 2.8. The cluster encompassing the left basal ganglia extended from left orbitofrontal cortex anteriorly, including medial orbital gyrus, olfactory sulcus, cingulate gyrus, posterior orbital gyrus, extending superiorly to putamen, globus pallidus, circular insular sulcus, ventral pallidum, nucleus accumbens, anterior perforated substance, posterior hypothalamus (Figure 2.9), head of caudate nucleus and subcallosal cortex. The cluster was constrained by the lateral border of putamen, extending posteriorly towards long insular gyrus and bounded posteriorly by the posterior borders of putamen, globus pallidus and pallidum, extending ventrally to include left amygdala, hippocampus and parahippocampal gyrus. The peak Z-scores and MNI coordinates of these regions are shown in Table 2.4.

Figure 2-8 Nuclei within the basal ganglia showing increases in rCBF prior to a GONB. rCBF increases at baseline are indicated in yellow (cluster corrected, $p < 0.05$), whilst masks of nuclei within the basal ganglia are illustrated in blue.
rCBF = regional cerebral blood flow, GONB = greater occipital nerve block

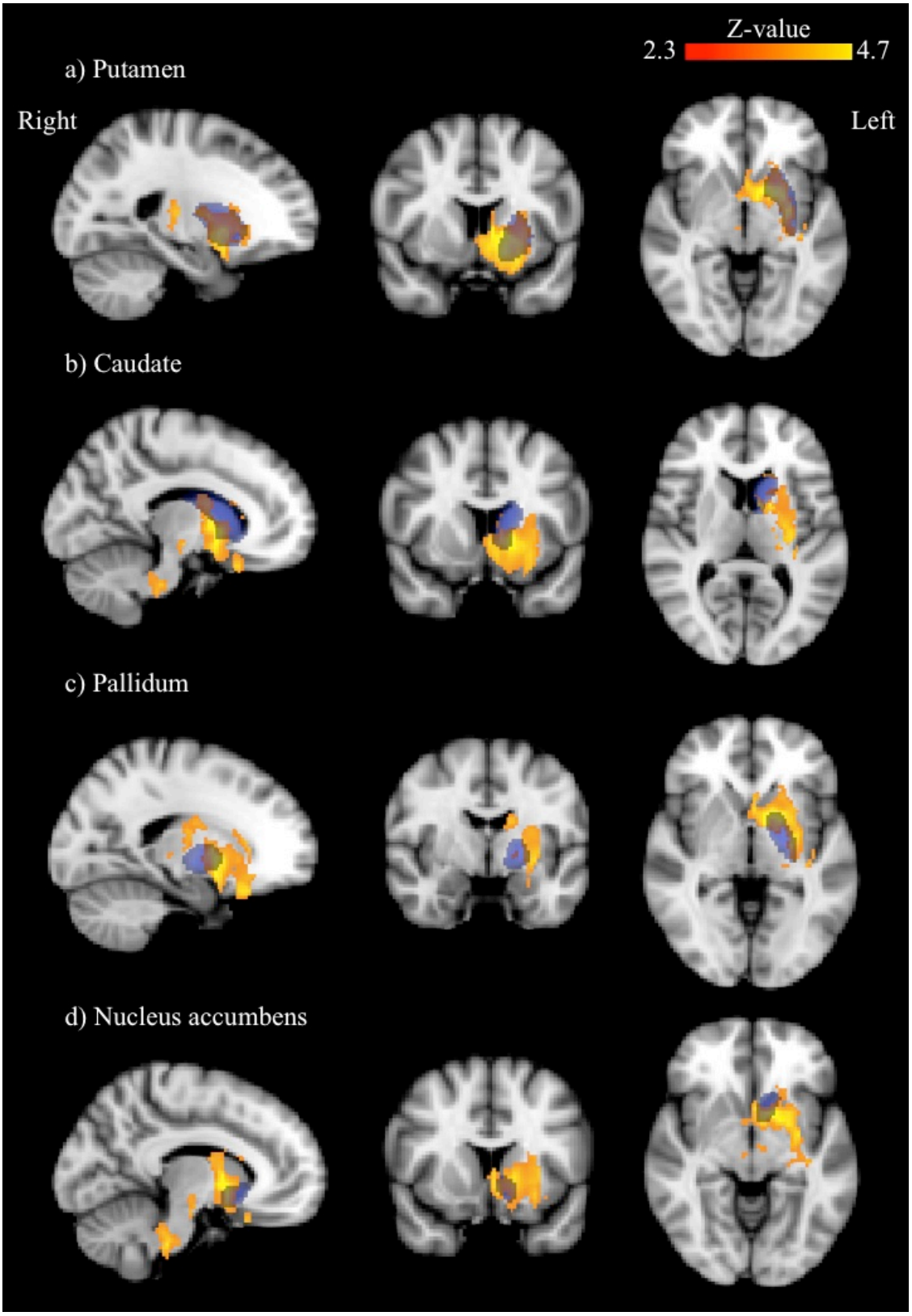
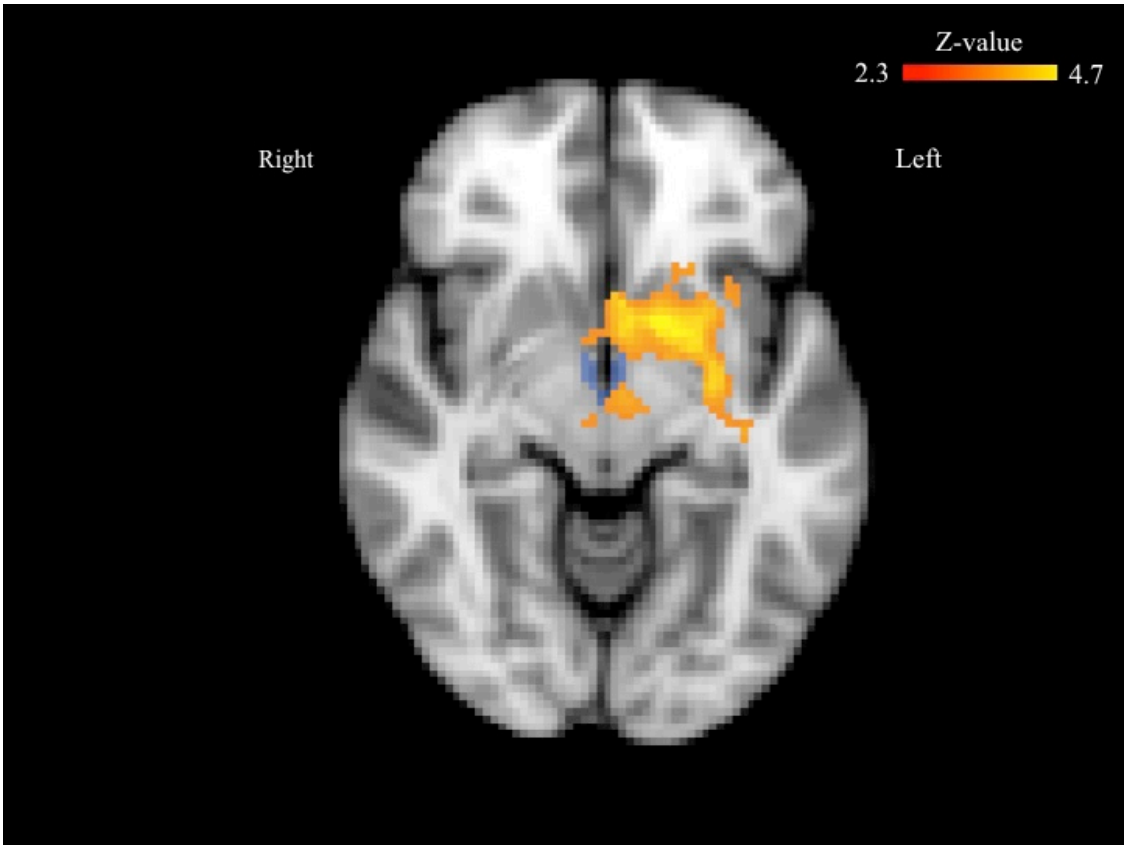


Table 2-4 Regions showing increased regional cerebral blood flow during the interictal period prior to the GONB

Structure	Peak Z-stat	Cluster Volume	MNI Coordinates		
			x	y	z
Left Putamen	4.73	6125	-16	8	4
Left Globus Pallidus	4.49	7508	-12	10	-2
Left Caudate	4.44	1794	-12	10	0
Left Pons	4.26	11983	-2	-12	-22
Left Ventral Pallidum	4.06	870	-14	8	-13
Left Long Insular Gyrus	3.81	928	-29	-17	14
Left Amygdala	3.71	1244	-25	10	-14
Left Inferior Frontal Gyrus	3.64	916	-18	24	-20
Left Middle Frontal Gyrus	3.62	56	-19	26	-20
Left Head of Caudate Nucleus	3.49	296	-2	14	-4
Right Inferior Colliculus	3.33	216	10	-33	-19
Left Parahippocampal Gyrus	3.26	297	-30	-8	-14
Left Thalamus	3.12	255	-22	-20	10
Left Medial Frontal Gyrus	3.10	86	-12	24	-20
Left Rectal Gyrus	3.09	16	-10	22	-22
Left Locus Coeruleus	3.09	108	-9	-33	-28
Left Superior Temporal Gyrus	3.02	32	-35	-26	6
Left Transverse Temporal Gyrus	2.95	44	-33	-26	10
Red Nucleus (midline)	2.90	30	0	-13	-8
Left Posterior Hypothalamus	2.90	5	0	-12	-8
Left Nucleus Accumbens	2.77	24	4	6	-2
Left Orbital Gyrus	2.76	24	-14	24	-26
Left Parahippocampal Gyrus	2.65	2	-21	10	-21
Left Cerebellar Tonsil	2.58	1	-11	-33	-45
Left Subcallosal Cortex	2.52	64	2	18	4
Right Cerebellar Tonsil	2.30	4	12	-34	-45

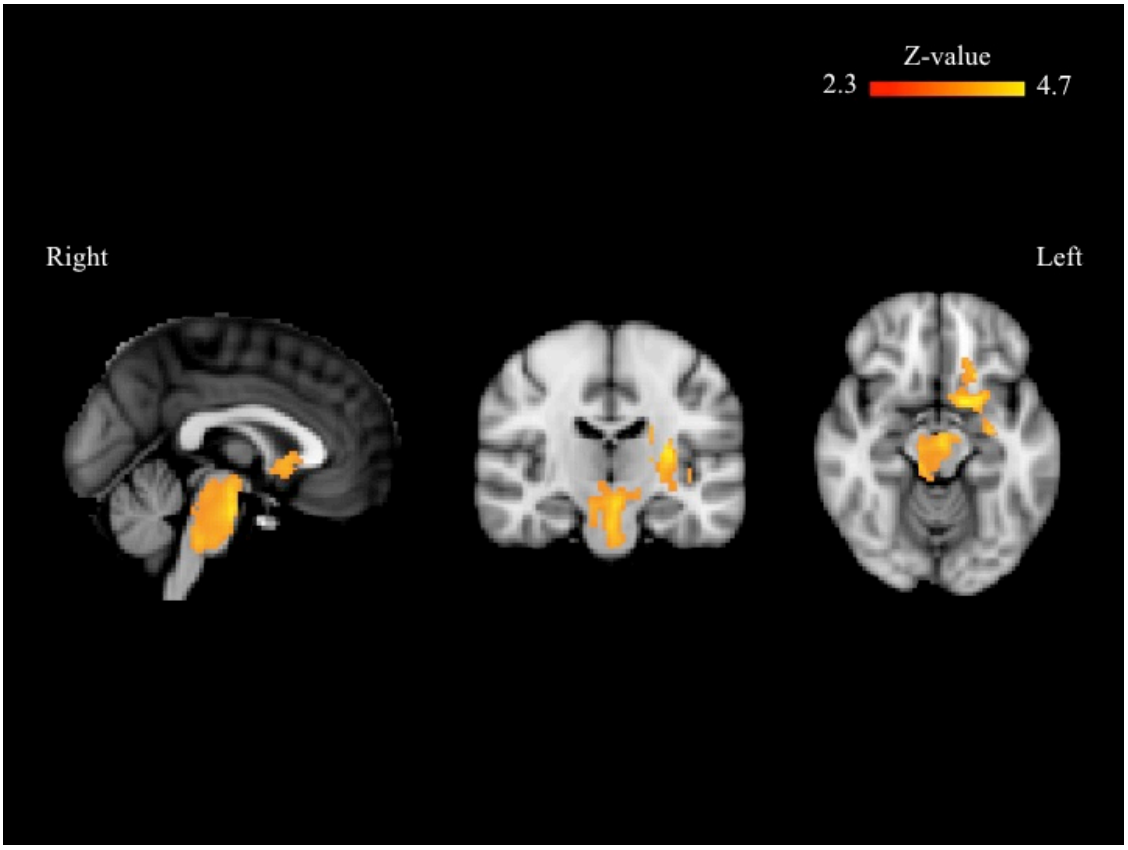
Each location indicates voxel with highest Z-stat score within the cluster ($p < 0.05$)
Coordinates presented are in MNI space.
GONB = greater occipital nerve block, MNI = Montreal Neurological Institute

Figure 2-9 Hypothalamic activation observed during the interictal state. Axial view showing significant increases in rCBF (cluster corrected, $p < 0.05$) within the left basal ganglia and the left posterior hypothalamus (hypothalamic mask illustrated in blue).
rCBF = regional cerebral blood flow



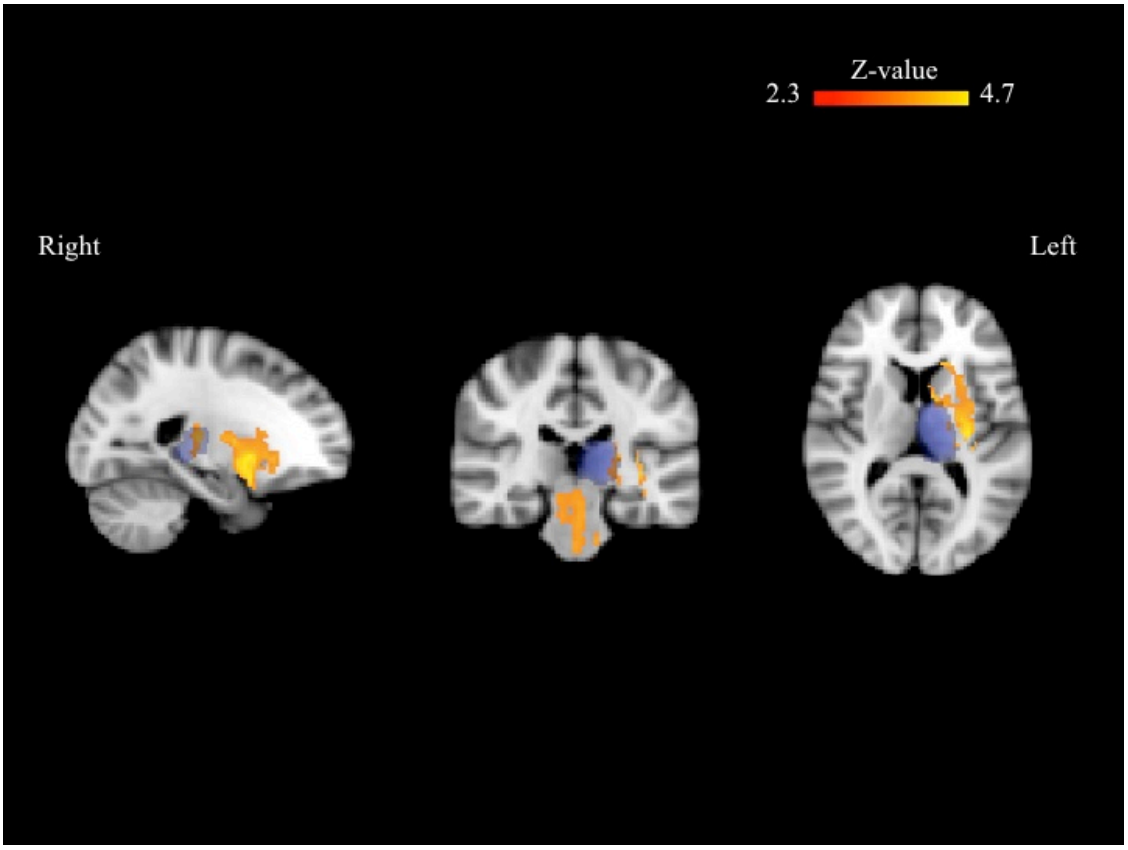
Within the brainstem, bilateral increases in rCBF were observed which extended superiorly from the red nucleus, including substantia nigra, crus cerebri, basilar pons, pontine nuclei, medial leminiscus, right inferior colliculus and locus coruleus, extending inferiorly to right superior cerebellar peduncle and right central tegmental tract, crossing the midline to include left middle cerebellar peduncle (Figure 2.10).

Figure 2-10 Cluster corrected statistic map showing significant increases in rCBF in the brainstem prior to the GONB. Bilateral increases in rCBF (shown in yellow) seen in red nucleus, substantia nigra and pons.
GONB = greater occipital nerve block, rCBF = regional cerebral blood flow



A narrow strip of cluster was also seen in the left ventral posterolateral thalamic nuclei that extended to the lateral borders of left lateral posterior thalamic nucleus and pulvinar nucleus prior to the GONB, as shown in Figure 2.11.

Figure 2-11 Significant rCBF increases in the left thalamus before the GONB (cluster corrected, $p < 0.05$) shown in yellow whilst mask of thalamus is illustrated in blue
GONB = greater occipital nerve block, rCBF = regional cerebral blood flow



Meanwhile, following the GONB, there were several discrete clusters indicating significant increases in rCBF identified in left superior frontal gyrus and sulcus, left middle frontal gyrus, right superior temporal gyrus, bilaterally in middle and inferior temporal gyri, left superior parietal gyrus and bilaterally within the occipital cortex in inferior, fourth, middle and superior orbital gyri, including intraparietal and calcarine sulci, as shown in Figure 2.12. The peak Z-scores and MNI coordinates of these regions are shown in Table 2.5.

Figure 2-12 Lightbox view showing post-GONB increases in rCBF observed bilaterally in several brain cortices. Cluster corrected Z-statistical maps ($p < 0.05$) showing significant increases in rCBF (shown in yellow) in frontal, temporal, parietal and occipital cortices after having the GONB

GONB = greater occipital nerve block, rCBF = regional cerebral blood flow

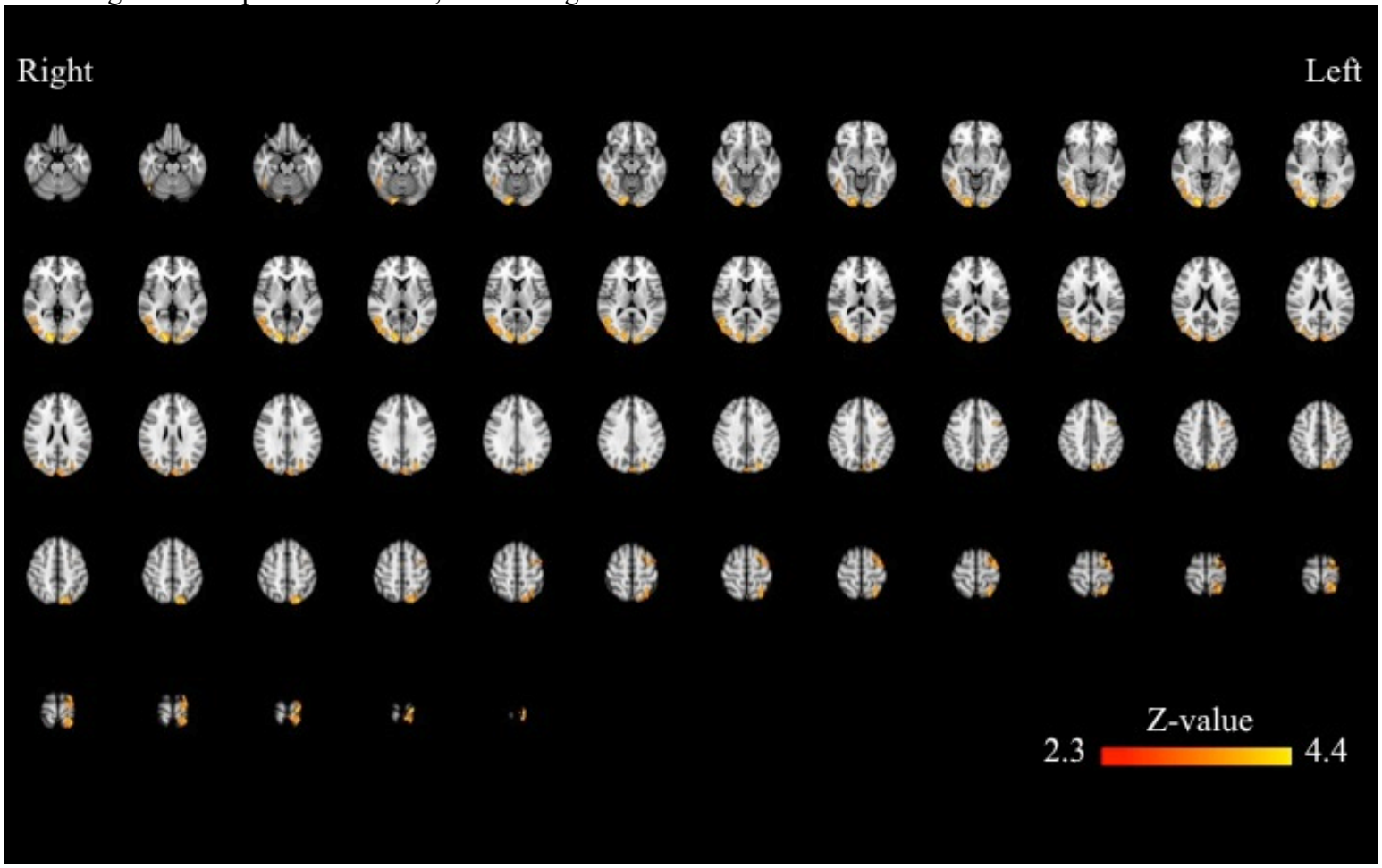


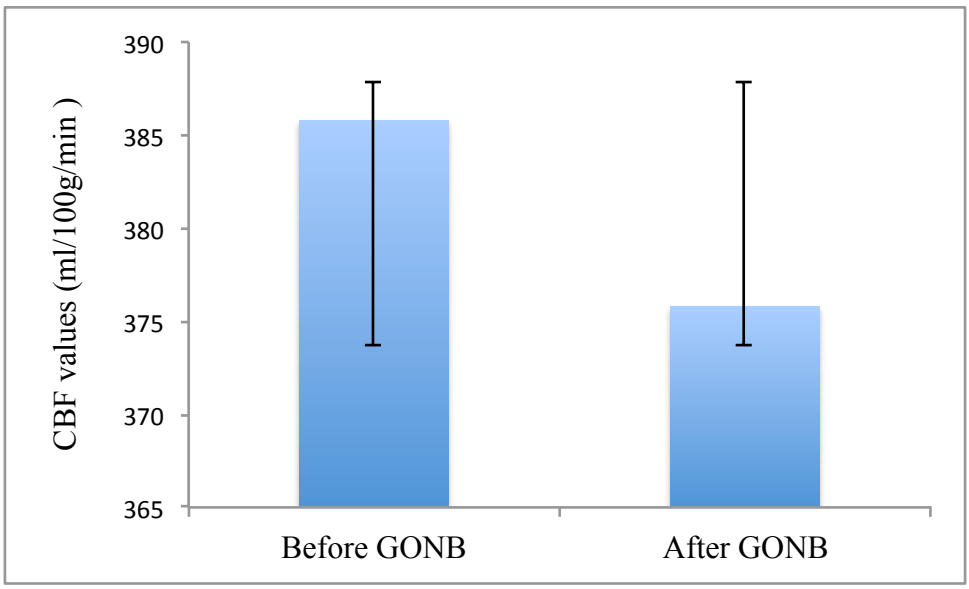
Table 2-5 Regions showing increased regional cerebral blood flow during the interictal period following the GONB

Structure	Peak Z-stat	Cluster Volume	MNI Coordinates		
			x	y	z
Right Superior Occipital Gyrus	4.44	4466	20	-86	2
Right Lingual Gyrus	4.29	2652	20	-88	-2
Right Superior Temporal Gyrus	4.25	1872	46	-60	20
Right Inferior Occipital Gyrus	4.23	504	20	-91	-13
Left Middle Occipital Gyrus	4.23	2694	-32	-80	4
Right Middle Temporal Gyrus	4.18	5070	58	-64	12
Right Fusiform Gyrus	4.00	500	18	-91	-18
Left Precuneus	3.98	3904	-9	-68	68
Left Cuneus	3.87	4553	-12	-94	4
Right Middle Occipital Gyrus	3.84	4306	40	-84	8
Left Sub-Gyral	3.80	954	-28	-82	-1
Left Superior Frontal Gyrus	3.75	876	-22	4	70
Left Lingual Gyrus	3.68	740	-12	-100	-9
Left Middle Frontal Gyrus	3.66	2344	-25	4	70
Left Superior Parietal Lobule	3.65	3072	-30	-68	62
Left Precentral Gyrus	3.65	674	-16	-28	82
Right Sub-Gyral	3.62	2144	22	-94	-4
Left Postcentral Gyrus	3.48	2414	-24	-44	76
Left Paracentral Lobule	3.26	200	-8	-42	80
Right Superior Occipital Gyrus	3.24	304	36	-76	26
Left Superior Occipital Gyrus	3.22	206	-30	-81	30
Right Angular Gyrus	3.20	112	36	-77	28
Right Inferior Temporal Gyrus	3.14	450	44	-72	-1
Left Angular Gyrus	3.05	36	-33	-78	28
Left Inferior Parietal Lobule	3.01	44	-33	-54	60
Right Declive	2.96	10	46	-66	-21
Right Precuneus	2.89	120	4	-86	40
Left Middle Temporal Gyrus	2.87	300	-34	-80	16
Right Supramarginal Gyrus	2.74	100	50	-58	30
Left Inferior Occipital Gyrus	2.74	188	-14	-94	-13
Left Fusiform Gyrus	2.52	18	-24	-94	-18
Cuneus (midline)	2.51	8	0	-88	26
Left Medial Frontal Gyrus	2.39	14	-5	-28	82
Left Inferior Temporal Gyrus	2.34	3	-37	-74	-2

Each location indicates voxel with highest Z-stat score within the cluster ($p < 0.05$)
Coordinates presented are in MNI space.
GONB = greater occipital nerve block, MNI = Montreal Neurological Institute

Based on our *a priori* hypothesis of reductions in rCBF in the hypothalamus following the GONB, we compared the mean rCBF in the left hypothalamus across patients between the two scanning sessions. This showed that there was a reduction in rCBF following the GONB, as shown in Figure 2.13, although this did not reach statistical significance; $t(11) = 0.78$, $p = 0.45$.

Figure 2-13 Difference in mean rCBF before and after the GONB in left hypothalamus. Error bars represents standard deviation.
GONB = greater occipital nerve block, rCBF = regional cerebral blood flow



2.4 Discussion

Significant increases in rCBF were identified in several brain structures of CH patients prior to the GONB, which were subsequently reduced at the follow-up scanning session, following response to the GONB. Of particular interest was the increase in rCBF in the left posterior hypothalamus, which is a structure that has been implicated to have a pivotal role in CH pathophysiology, thus supporting the hypothesis made of change in rCBF in this region following treatment. Moreover, significant increases were also observed in the left orbitofrontal cortex, left basal ganglia, left amygdala, left hippocampus and parahippocampal gyrus, left lateral posterior thalamic and pulvinar nuclei and bilaterally in the brainstem. Similar findings have been reported in previous neuroimaging studies in CH patients, with activations reported in the orbitofrontal cortex, ipsilateral inferior/posterior hypothalamus, ipsilateral basal ganglia and ipsilateral/contralateral posterior thalamus, although in those studies, patients were scanned during spontaneous or triggered attacks (18, 19, 37). On the

other hand, patients in this study were scanned during the interictal state, thus it begs the question of whether these structures actually have an important role in the pathophysiology of CH.

Neuroimaging studies in CH have led to advances in our understanding of the underlying mechanisms in this disorder, specifically the potential role of the hypothalamus as the central generator of CH (18, 19, 29, 37). A recent study has shown that hypothalamic activation persists even between attacks in CH patients following occipital nerve stimulation (ONS) (217). Our study supports this observation of activation of the posterior hypothalamus in CH patients during the interictal state. Interestingly, the significant increase in rCBF was only observed in the left posterior hypothalamus, possibly echoing the higher proportion of patients who had left sided attacks that were recruited in this study, thereby likely reflecting ipsilateral posterior hypothalamic activation. However, future work will need to be done to ascertain this finding, as will be discussed in Chapter 6.

Magis and colleagues performed an ^{18}FDG-PET (fluorodeoxyglucose-positron emission tomography) study in between attacks in CCH patients who underwent ONS and found significant hypermetabolism in ipsilateral hypothalamus, ipsilateral pulvinar and brainstem compared to healthy controls (217). The brainstem has previously been found to be consistently activated in migraine and was therefore suggested to have a crucial role in its pathophysiology (218, 219). However, brainstem activations have also been observed in CH and in hemicrania continua (HC), whose clinical phenotype overlaps with both migraine and the trigeminal autonomic cephalalgias (TAC) (44, 156, 217). The brainstem activations seen in previous CH studies included ipsilateral trigeminal root entry zone, the bilateral red nucleus and ventral pons, whereas in HC, activations were observed in ipsilateral

dorsal rostral pons, extending to the red nucleus and substantia nigra (44, 156). Additionally, there has been a single report of brainstem activation in spontaneous attacks of SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), which also belongs to the TACs (220).

Taking into account the hypothesized involvement of the trigeminal-autonomic reflex in the pathophysiology of TACs, including CH, this brainstem activation has been postulated to represent the connection between the caudal part of the trigeminal nucleus and the hypothalamus, even though Morelli and colleagues speculated that given the role of these structures in motor function, it may equally be associated with a defence "fight-or-flight" mechanism, which is characteristic of CH (156, 220). Therefore, whilst the brainstem may have a role as the possible generator in migraine, it may reflect the functional connectivity between the spinal trigeminal nucleus and hypothalamus in CH and the TACs. Unfortunately, the trigeminal nucleus caudalis cannot be visualized in this study, as the imaging volume did not extend inferiorly to this portion of the hindbrain.

The increase in rCBF in the basal ganglia is also of particular interest. The basal ganglia are composed of a number of subcortical nuclei including caudate nucleus and putamen (often collectively termed as striatum), globus pallidus and substantia nigra (221). The substantia nigra is the main source of dopamine in the brain, which is one of the principal neurotransmitters within the basal ganglia. The basal ganglia is now known to play a role in pain processing and in particular, is involved in the sensory-discriminative, affective/emotional and cognitive dimensions of pain, as well as having a role in pain modulation and acting as a gating mechanism to regulate transmission of nociceptive information to higher centres (222). The basal ganglia is well connected to all cortical areas, including hippocampus, amygdala and thalamus

and receives nociceptive information from two major sources (221, 223). From the spinal cord and brainstem, the basal ganglia can receive afferent inputs via direct (e.g. spino-basal ganglia) or indirect (e.g. spino-thalamic-basal ganglia) pathways, whilst inputs from cortical and subcortical brain regions are transmitted via the basal ganglia-thalamic-cortical loop (221). Cortical regions within this loop are known to have important roles in pain processing, including the anterior cingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, insula and hippocampal regions (221).

Neuroimaging studies in migraine have recently suggested the possible involvement of the basal ganglia in the pathophysiology of the disorder. These studies have shown structural and functional brain changes in the basal ganglia associated with migraine (223-226). In particular, increases in rCBF in the basal ganglia have been reported in migraneurs during a spontaneous headache attack, with decreased grey matter density in the globus pallidus and putamen, which correlated with disease duration and attack frequency respectively (224, 226). Decreased volumes in the caudate and nucleus accumbens have also been reported in migraineurs compared to healthy controls, which was negatively correlated to disease duration (225). Furthermore, they found an interictal increase in resting state functional connectivity in migraineurs compared to healthy controls, with increased connectivity between the caudate and nucleus accumbens with several brain areas known to be involved in nociceptive and sensory processing, specifically putamen, parahippocampal gyrus, insula, amygdala, orbitofrontal cortex, and anterior and posterior cingulate cortices (225). Conversely, an increase in grey matter volume in the caudate nucleus has been observed in migraineurs with high attack frequency (8-14 headache days per month) compared to those with low attack frequency (1-2 headache days per month), with increased

functional connectivity between the basal ganglia (putamen and pallidum) and anterior insula, temporal lobe and hippocampus, and reduced connectivity between caudate and middle frontal cortex and pallidum (223).

It is also noteworthy that dopaminergic involvements have also been reported from PET studies in chronic orofacial pain conditions, specifically burning mouth syndrome and atypical facial pain. In the former, decreased dopaminergic function in the putamen was observed, whereas in the latter, there was an increased availability of dopamine receptors in the putamen in patients compared to healthy controls (221). Therefore, taking these studies into account, it is likely that the recurring activations of ipsilateral basal ganglia seen in neuroimaging studies in CH may actually be suggestive of its important role or the role of the dopaminergic system in CH pathophysiology.

Several lines of evidence support our hypothesis of an impaired dopaminergic system in CH. There have been reports of dopamine antagonists, such as Olanzapine, Clozapine and Chlorpromazine in the acute and preventative treatment of CH as well as recurrence of CH attacks with initiation of Pramipexole, a dopamine agonist (227-230). Moreover, increased levels of platelet dopamine have been found in ECH patients, both during and outside of a bout (231). Furthermore, since dopamine exerts an inhibitory effect on prolactin release, blunted 24-hour prolactin production in CH patients during a bout and in remission, with reduced response to thyrotropin-releasing hormone, provides clues to the possible impairment within this system (232). A recent study found impaired increase in growth hormone levels following an apomorphine challenge in CH patients outside a bout, suggesting decreased sensitivity of dopaminergic neurons (233).

From a clinical point of view, dopamine is known to have a major role in regulation of physical movement, thus an imbalance may account for the restlessness and agitation that is usually associated with CH attacks, whereby patients often report inability to sit still. Moreover, the role of dopamine in addiction may somewhat explain the addictive personality traits that are seen in CH patients, whereby they have a tendency to consume high quantities of cigarettes and caffeine (234). Taken together, these findings suggest possible involvement of the dopaminergic system in CH.

Thus, most of the areas found to show significant increases in rCBF in this study are also activated in other pain disorders, including migraine and TAC, and in ongoing clinical pain. Since pain is known to be a multidimensional experience, these structures may form a system or integrated network of brain regions that encodes nociceptive information of CH, in particular the sensory-discriminative, affective/emotional and cognitive dimensions of the pain experience. Contrary to other pain neuroimaging studies and previous studies on CH, no activations were observed in other regions such as anterior cingulate cortex, primary and secondary somatosensory cortices, prefrontal cortex or cerebellum, possibly because these regions are more involved in the processing of acute pain (195, 216).

However, even though these structures are acknowledged to have roles in the processing of pain, they are also accepted to be multifunctional and known to be associated with attention, emotion/motivation-affect, decision-making, sensory perception, motor function and cognition in general (235-237). Thus, whilst it is not discounted that they may be involved in pain processing, their multifunctional roles challenges the belief that activity within this network is purely driven by pain and that the changes seen are exclusively related to or caused by it, but likely reflects a salient response (235-237). This serves to assist attentional systems, preparing the body to

respond to potentially threatening stimuli, and as such, forms an important attribute to the pain experience (235-237). In CH, increased rCBF within this functionally coupled network may suggest a state of heightened awareness in anticipation of the next imminent attack.

It is now known that the brain is plastic in nature, with the ability to adapt both structurally and functionally to incoming stimuli (238-244). Such changes can be seen in chronic pain disorders whereby structural imaging studies, specifically VBM, have demonstrated changes in grey matter volume in distinct brain regions, namely the orbitofrontal cortex, insula, cingulate cortex and dorsal pons, suggesting a common basis (238). A recent VBM study in CH has reported similar grey matter changes in chronic sufferers, with both increased and decreased volumes observed in ECH patients in a bout, whilst those outside a bout had the least marked changes (245). Interestingly, there is a degree of overlap in the structural abnormalities from the VBM study with the changes seen in this study, thus supporting the concept of neuroplastic change in CH patients whereby repeated attacks can lead to a dynamic change even in the absence of pain.

Meanwhile, the subsequent reductions in rCBF seen following the GONB may reflect a winding down of this system, as was observed in patients with paroxysmal hemicrania following indomethacin (246). Matharu and colleagues postulated that the central structures that are important in generating an attack are relatively activated during the interictal state but at subthreshold level for pain generation, with an attack being triggered once a threshold for pain is reached (246). The same mechanism is likely to exist in CH, with the GONB having a potent effect in deactivating this excitable system, possibly through neuroplastic changes. Indeed, neuroplasticity is

known to be a dynamic process and there have been reports of reversal of grey matter abnormalities following pain relief in several chronic pain disorders (241, 247). Furthermore, our psychometric results showed a trend for improvement of anxiety and depressive symptoms in our patient cohort. Thus, as it is clear that some of the structures, like the insula, amygdala and parahippocampal region, are involved in processing affect and emotions, the changes seen following treatment may partly be attributed to this finding. Hence, it may be important in future studies to compare the clinical, psychometric and neuroimaging endpoints together, possibly by performing a regression analysis to account for this factor.

At present, any explanations for the increased rCBF observed in the frontal, temporal, parietal and occipital cortices following the GONB are highly speculative. The fairly large representation in the occipital cortex is surprising, particularly since the patients did not receive any visual stimuli during scanning and scans were performed in a dark room. Therefore, it is postulated that these activations may be associated with relief of pain following treatment. A previous fMRI study looking at neuronal specificity of acupuncture response showed several areas of activation, which included brain regions involved in pain processing, as well as parts of the occipital, temporal and parietal cortices, which they postulate may be associated with the functional organization of thalamo-cortical relays related to acupuncture-induced analgesia (248). Further work comparing responders and non-responders to the GONB will need to be undertaken to shed light on the interpretation of this finding.

The main limitation of this neuroimaging study was the small sample size, which is considered borderline for detecting significance in fMRI studies. This is more so when one takes into account that three of the patients did not respond to the GONB. Hence,

the study was unable to make a comparison between responders and non-responders, which would have allowed us to make a better judgment of the effects this treatment has on brain function. Due to this small sample size and the large heterogeneity within the sample, the analysis of the psychometric data was largely underpowered, thus a descriptive statistical approach was undertaken to present the findings. Another limitation is the possible confounding order effect that due to methodological difficulties could not be controlled for. Due to the design of the study, whereby patients were scanned before and after they have had a GONB, it was not possible to randomize the order of the scans. However, considering the findings from this study, whereby the structures activated were those that are known to be involved in pain processing, it is unlikely that this was a significant confounding factor. Furthermore, to the best of my knowledge, there have been no previous reports of rCBF changes that were specific to and involved a considerable number of structures relating to pain processing.

This study has identified several structures that show increases in rCBF during the interictal period in CH patients, with subsequent reductions following the GONB. This includes the posterior hypothalamus, which has been long been suspected to have a role in CH pathophysiology. However, of more interest are the changes seen in the basal ganglia and brainstem, which although have also been reported in previous studies, have often been overlooked as structures involved in the general processing of pain. Whilst the roles of these structures in the pathophysiology of CH remain unknown, the fact that they were activated in the headache-free state suggests that they may have pivotal roles in the underlying mechanisms of this highly disabling disorder.

Chapter 3 Saccadometry study

3.1 Introduction

The study of saccadic latency in a number of neurological disorders has demonstrated its potential of being used as a biomarker to aid in diagnosis and monitoring of disease progression and response to treatment. In Huntington's disease for example, which is a neurodegenerative disorder, saccadometry has been shown to have good discriminative power, being able to distinguish presymptomatic and symptomatic patients from healthy controls (70). Moreover, with the use of more challenging saccadic tasks, presymptomatic patients can be differentiated from the symptomatic group, with the added possibility that it may also be able to predict the onset of symptoms in the former clinical group (71). Furthermore, saccadometry has been tested in patients with Parkinson's disease who underwent subthalamic nuclei stimulation, and has been shown to be a useful tool in providing objective measures of treatment outcome (72). Similarly, it may provide a useful measure of cognitive fitness following anaesthesia (249).

Within the headache field, saccadic latency studies have only been used to investigate migraine, with earlier studies failing to provide evidence for differences between migraine groups and between migraineurs and controls (79, 80). However, later studies demonstrated that there were significant differences in saccadic latency between migraineurs and controls (75, 78). In particular, migraineurs had longer latencies with high variability in their reaction time compared to controls, and more errors made looking in the wrong direction (78). On the other hand, another study using the same protocol as will be described for our study, found smaller variability in saccadic latency distributions between migraineurs and

controls, with significantly less early saccades generated by the former (75). These differences may be attributed to methodological differences between the two studies, specifically the different saccadic tasks employed. To the best of our knowledge, studies of saccadic reaction time in other headache disorders have not been evaluated.

Owing to the success of saccadometry in the investigation of these various neurological disorders and the simplicity of both the task itself and the collection of large data sets, a study of saccadic reaction time in CH patients was performed, with the hope that it will improve our understanding of the underlying mechanisms of this disorder. Thus, the aim of this study was to investigate for possible differences in cross-sectional reaction time distributions of horizontal saccadic eye movements between CH patients and age- and sex- matched controls.

3.2 Methods

3.2.a Subjects

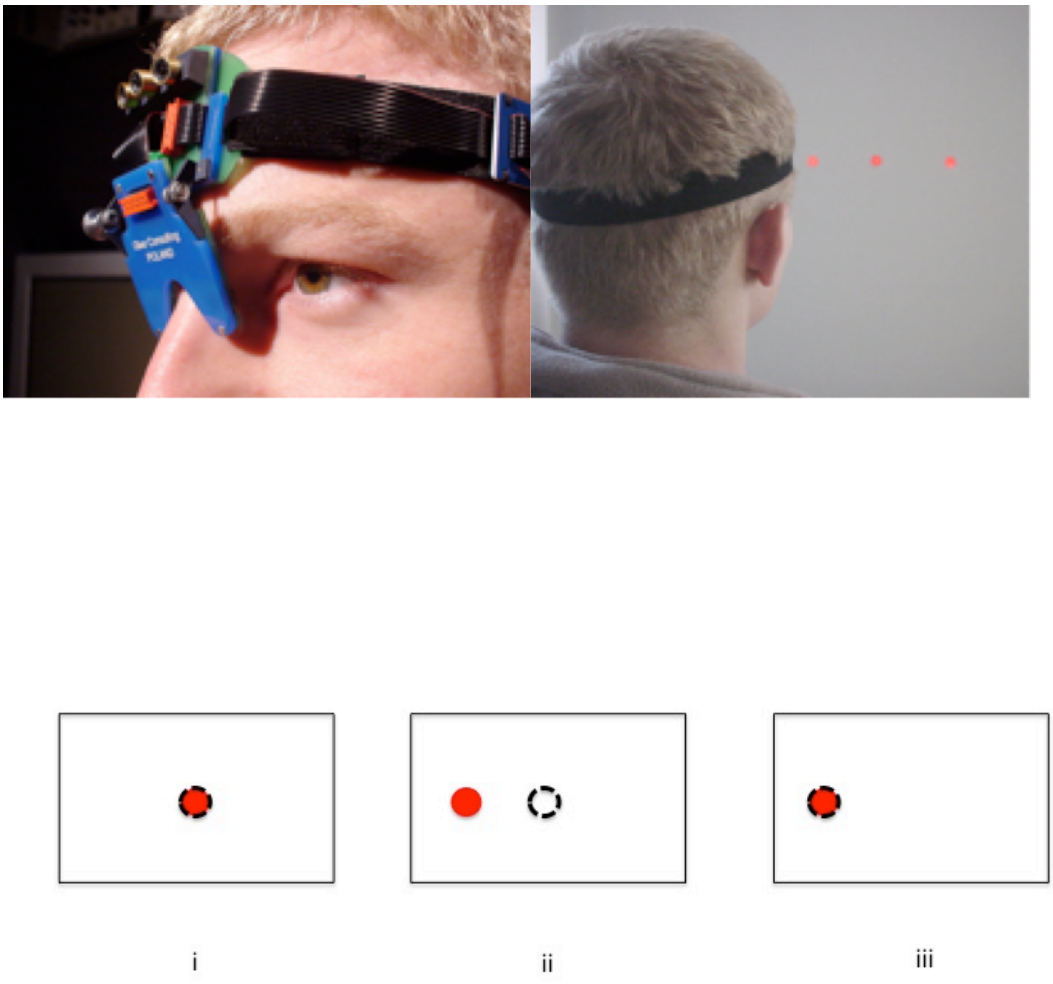
Forty-two patients who attended the headache clinic at The National Hospital for Neurology and Neurosurgery, London and satisfied the ICHD-II diagnostic criteria for CH were recruited into the study (7). Ethical approval for the study was obtained from the South East Research Ethics Committee. Informed consent was obtained from all patients prior to commencement of the study. Age- and sex-matched controls were taken from a pre-existing database of a recent study using the same protocol.

3.2.b Data acquisition

Saccadic latency recordings were made using a miniaturised, head-mounted, non-invasive, infrared reflection oculometer (12-bit resolution, sampling rate 1kHz,

low-pass filtered at 250 Hz, signal-to-nosie ratio 45 dB), as shown in Figure 3.1. Since the recording device is head-mounted, the target display moves with head movement and thus no head restraints were required. The oculometer has three low-power red lasers that projected high contrast 13 cd m-2 target dots onto a light-coloured background, subtending 0.1°, in a horizontal line at ± 10° to the midline; to a first approximation these angles are independent of the distance between subject and background. The study was carried out in the clinical setting, with patients seated one metre from a blank, non-reflective wall, with minimal auditory or visual stimuli (in a non sound-proof room). Two sets of 100 saccadic horizontal eye movements were recorded for each patient. Each set of trial began with a self-calibration process, with ten preliminary trials to either side, followed by the actual run. This consisted of presentation of a central target, onto which the patients fixated. After a random fore period of 1 - 2 seconds, this central target disappeared and jumped either to the left or right (chosen at random to avoid anticipation). The patients were instructed to track the moving target with a saccade. Depending on the patients' response, the target remained for 200 milliseconds after the end of the resultant correct saccade, or in the case of an incorrect or absent response, for 1 second, whichever was the shorter. Patients were instructed to track the movement of the target with their eyes as quickly as possible without compromising accuracy. Only one clinical visit was required for the study.

Figure 3-1 Oculometer in situ and in use



Above, clinical photographs of oculomotor in use. Below, schematic illustration of study task, showing (i) the central fixation target (red circle), which after a random foreperiod of 1–2 seconds, disappeared and jumped randomly to the left or right. Patients were required to track this target with a saccade (dashed ring indicates fixation on target. Adapted from Chandna and colleagues (75).

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3.2.c Inclusion and exclusion criteria

- Male or female CH patients
- Aged between 18 and 60 years in good general health apart from suffering from headaches.
- Diagnosis of CH according to ICHD-II diagnostic criteria.
- Must not have any other neurological disorder such as stroke, multiple sclerosis, epilepsy, psychiatric disorders, visual disorders or concussion within the past year.
- Not on any CH prophylactic medication or antidepressants, currently or in the last month.
- No headache during testing.

3.2.d Data Analysis

The recorded saccadic latency measurements were downloaded from the oculometer to a PC using LatencyMeter, a program that automatically triages data by eliminating trials with aberrant profiles due to blinks, head movements, inattention etc. Following this preprocessing step by LatencyMeter, it was then exported to SPIC (Saccadic Programming and Instrumentation Computer), the latency analysis software.

Saccadic latency varies between trials randomly, but produces a skewed distribution when plotted as a histogram. However, the reciprocal of latency usually follows a normal distribution, whose best-fit values of mean μ and standard deviation σ can be estimated within SPIC by minimisation of the Kolmogorov-Smirnov statistic. Some patients also show a small subset of early saccades of unexpectedly short latency, which can be described by its standard deviation, σ_E.

Thus, the entire distribution for each patient can be completely described by just 3 parameters - μ, σ and σ_E. Each parameter can then be compared between the CH population and the control population using parametric and non-parametric tests where appropriate using a significance level of $p < 0.05$ in all cases.

3.3 Results

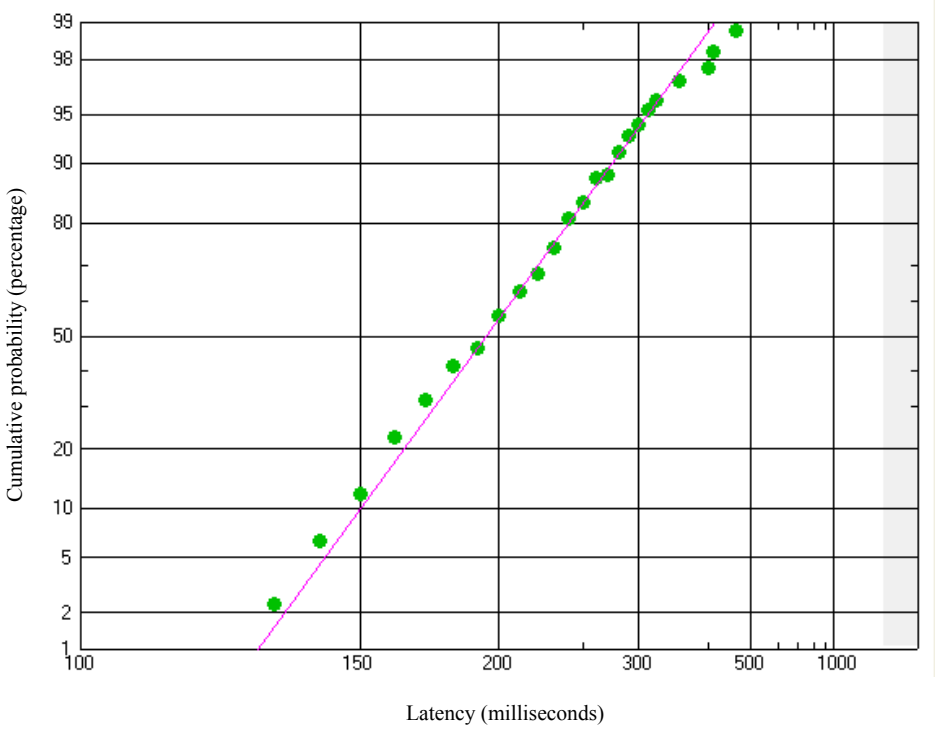
3.3.a Subjects

There were 35 males and 7 females in the CH patient group, with a mean age of 41.7 ± 11.5 years. The mean duration since onset of CH was 13.7 years (range 3 – 42 years). Meanwhile, the control group consisted of 20 males and 7 females, with mean age of 44.0 ± 14.5 years. There were no significant differences in age (two-sample *t*-test, $p = 0.498$) and gender ($p = 0.351$) between the CH patients and control groups.

3.3.b Recinormality of reaction time distributions

Using the SPIC software, Kolmogorov-Smirnov one-sample test demonstrated that the reaction time distributions of the CH patient group and control group did not differ significantly from a recinormal distribution ($p > 0.05$), thus supporting the LATER model and the use of the three parameters (μ, σ and σ_E) to describe the reaction time distributions. An example of a reciprobit plot from a CH patient is shown in Figure 3.2.

Figure 3-2 A reciprobit plot showing the recinormal distribution of saccadic reaction time of a cluster headache patient



3.3.c Reaction time distributions between left and right saccades

The Shapiro-Wilk test was performed to assess normality of the reaction time distributions, which revealed that μ followed a normal distribution, whilst σ and σ_E departed significantly from normality. Therefore, a two-sample *t*-test was performed to compare differences in mean between saccades made to the right direction and those made to the left. This showed that there were no significant differences in mean saccadic latency with respect to the direction of the saccade. Meanwhile, Mann-Whitney U test was performed to compare for differences in σ and σ_E between the two groups, which also showed no significant differences, as shown in Table 3.1. Thus, the averages of saccades made in both directions were used for analysis.

Table 3-1 Reaction time distributions of right and left saccades

Saccadic distribution parameters, mean ± SE (milliseconds)	Right saccade	Left saccade	p – value[1]
Mean saccadic latency, μ	5.61 ± 0.14 (	5.46 ± 0.15	0.471
Standard deviation of saccadic latency, σ	1.34 ± 0.08	1.32 ± 0.09	0.569
Standard deviation of early saccadic latency, σ_E	0.32 ± 0.16	0.32 ± 0.16	1.003

SE = standard error
[1]Based on two-sample *t*-test and Independent Samples Mann-Whitney U test

3.3.d Reaction time distributions between CH groups

Within the CH patient group, there were 17 patients who had the episodic variant, whilst 25 patients had CCH. Normality testing using the Shapiro-Wilk test revealed that all the three distribution parameters departed significantly from normality. Therefore, a Mann-Whitney U test was performed to compare the parameters between the two groups. There were no significant differences in any of the parameters of the reaction time distributions, as shown in Table 3.2. Thus, all CH patients were considered as a single group.

Table 3-2 Reaction time distributions of ECH and CCH patients

Saccadic distribution parameters, mean ± SE (milliseconds)	ECH	CCH	p – value[1]
Mean saccadic latency, μ	5.61 ± 0.23	5.52 ± 0.16	0.910
Standard deviation of saccadic latency, σ	1.38 ± 0.14	1.40 ± 0.11	0.960
Standard deviation of early saccadic latency, σ_E	0.56 ± 0.31	0.16 ± 0.16	0.157

SE = standard error, ECH = episodic cluster headache, CCH = chronic cluster headache

[1]Based on Independent Samples Mann-Whitney U test

3.3.e Reaction time distributions between male and female patients

There were 35 males and seven females in the CH group. Normality testing using the Shapiro-Wilk test showed that μ followed a normal distribution, whereas σ and σ_E departed significantly from normality. Therefore, two-sample *t*-test and Mann-Whitney U tests were performed to compare the parameters between the two groups respectively. There were no significant differences in any of the parameters of the reaction time distributions, as shown in Table 3.3, though due to the small sample size within the groups, this should be treated with caution.

Table 3-3 Reaction time distributions of male and female CH patients

Saccadic distribution parameters, mean ± SE (milliseconds)	Males	Females	p – value[1]
Mean saccadic latency, μ	5.51 ± 0.14	5.75 ± 0.33	0.521
Standard deviation of saccadic latency, σ	1.39 ± 0.10	1.40 ± 0.23	0.974
Standard deviation of early saccadic latency, σ_E	0.27 ± 0.15	0.60 ± 0.60	0.592

SE = standard error, CH = cluster headache
[1]Based on two-sample *t*-test and Independent Samples Mann-Whitney U test

3.3.f Reaction time distribution between CH patients and controls

The Shapiro-Wilk test for normality showed that μ conformed to a normal distribution, thus the two-sample *t*-test was used to compare for differences between the CH patient and control groups. On the other hand, both σ and σ_E deviated from normality, thus the Mann-Whitney U test was performed to compare differences in these parameters between the two groups. The results of this analysis are shown in Table 3.4.

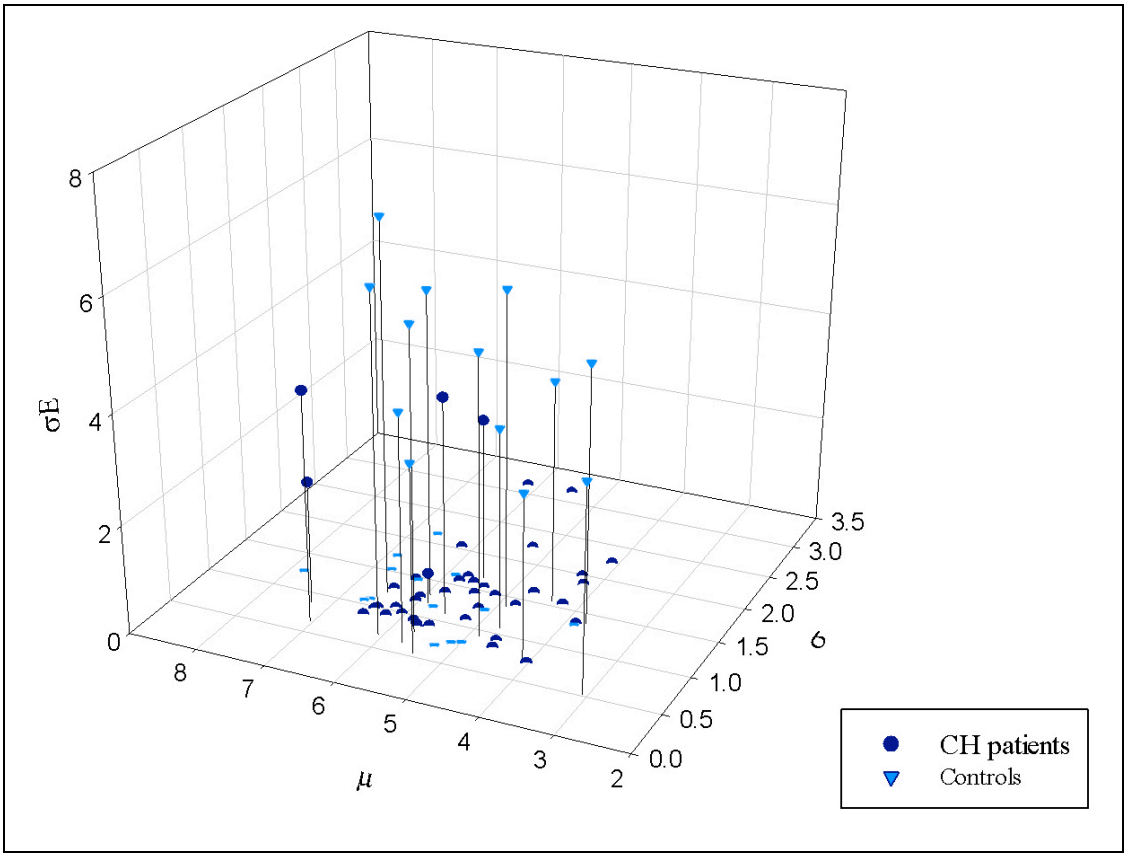
Table 3-4 Reaction time distributions of CH patients and controls

Saccadic distribution parameters, mean ± SE (milliseconds)	CH patients	Controls	*p* – value[1]
Mean of saccadic latency, μ	5.56 ± 0.13	5.02 ± 0.18	0.017
Standard deviation of saccadic latency, σ	1.39 ± 0.09	1.07 ± 0.07	0.005
Standard deviation of early saccadic latency, σ_E	0.34 ± 0.16	2.74 ± 0.53	<0.001

SE = standard error, CH = cluster headache
[1]Based on two-sample *t*-test and Independent Samples Mann-Whitney U test

There were significant differences in all three parameters between the CH patient group and the control group, as shown in Figure 3.3. For μ, CH patients had a significantly longer mean saccadic latency (5.56 ± 0.13) compared to controls (5.02 ± 0.18). Similarly, CH patients have a significantly higher σ (1.39 ± 0.09) compared to controls (1.07 ± 0.07).

Figure 3-3 A 3D scatter plot showing saccadic reaction time distributions of cluster headache patients and controls
CH = cluster headache, μ = mean of saccadic latency, σ = standard deviation of saccadic latency, σ_E = standard deviation of early saccadic latency



Meanwhile, only four CH patients exhibited an early saccade compared to 15 controls, which was considered to be statistically significant (Fisher's exact test for early saccades, $p < 0.001$). When considering only those individuals that exhibited an early saccade (4 CH patients, 15 controls), the Shapiro-Wilk test for normality revealed that their σ_E distributions was normally distributed. A two-sample *t*-test showed that there was a significant difference in the σ_E distribution ($p = 0.026$), with controls having a significantly higher σ_E (4.76 ± 0.32) compared to CH patients (3.38 ± 0.46).

3.3.g Log likelihood ratios for sensitivity and specificity

A binomial logistic regression analysis was performed to calculate log likelihood ratios (LLR) to predict the probability that an arbitrary saccadic reaction time distribution could be correctly or falsely attributed to the CH population. The formula generated was

$LLR = a\,\mu + b\,\sigma + c\,\sigma_E + d,$

where $a = 1.42$

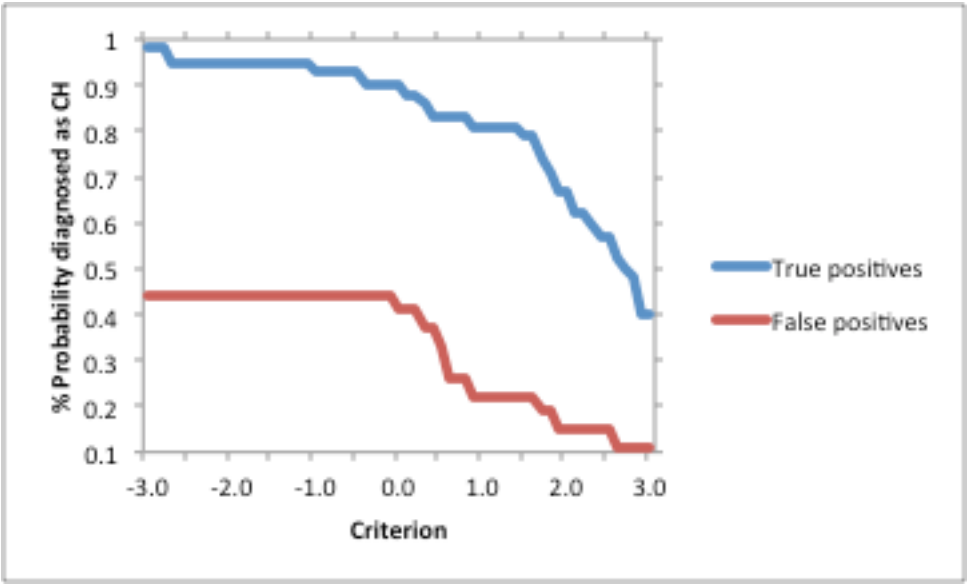
$b = 2.69$

$c = -1.36$

$d = -8.74$

From the above equation, σ proves to have the greatest weight, with μ and σ_E having nearly similar contributions to the LLR. A sensitivity/specificity plot (Figure 3.4) gives a visual representation of the good discriminative power of using saccadometry in CH, with optimum criterion LLR value of 0.9 yielding the best sensitivity and specificity values (81% true positives).

Figure 3-4 **Sensitivity/specificity plot showing percentage probability of being correctly diagnosed as having CH using saccadometry.** Percentage probability of being correctly diagnosed as having CH (y-axis) is plotted against the criterion LLR. CH = cluster headache



3.4 Discussion

To the best of my knowledge, this is the first study to examine saccadic reaction time in CH patients. Significant differences were found between the CH patient population and control group in their reaction time distributions. In particular, CH patients had a significantly longer mean saccadic latency with greater variability in reaction time compared to controls. Furthermore, a smaller proportion of CH patients exhibited an early saccade, with a reduction in the variability of reaction time of these early saccades, compared to controls.

Saccadic eye movement is controlled by a number of brain regions, which includes the superior colliculus (SC) that lies on the superior aspect of the brainstem, the basal ganglia (BG) and cerebral cortices (occipital, parietal and frontal) (250, 251). Visual input from the retina is conveyed to the SC, which triggers the oculomotor nuclei to initiate movement. However, the decision-making processes of the cerebral cortices and basal ganglia holds up this saccadic eye movement by exerting descending

inhibitory inputs to the SC, with movement being initiated only once a decision about "where to look" has been made. Thus, the SC constitutes the ''final common pathway'' for saccadic generation (250).

This finding of an increase in the mean saccadic latencies in CH patients suggests that saccadic information is processed at a slower rate in this population. A delay in the decision-making process can occur within any of the neural pathways involved in saccadic generation. However, the reduced proportion of early saccades in CH patients suggests the presence of a tight inhibitory control over the SC, with few spontaneous saccades managing to escape this control. Since the inhibitory input to SC stems mainly from the BG, it is therefore highly likely that this subcortical region is contributing to the impairment in saccadic reaction time distributions in this population. This correlates with the findings from the fMRI study (Chapter 2) that shows significant increases in rCBF in the BG during the interictal period, thus further supporting a possible role for this brain region to be involved in the pathophysiology of CH.

With regards to the increased variability in the reaction time distributions, there is neurophysiological evidence that links activity within locus coeruleus, which is a brainstem nucleus, to changes in σ (252). A previous study using the same protocol in a group of migraineurs found no differences in mean saccadic latency compared to controls, although there was reduced variability in saccadic latency distributions, with significantly less early saccades generated by the former (75). Since locus coeruleus is the principal site for noradrenaline synthesis in the brain, the authors hypothesized that this may reflect a functional deficit in the noradrenergic systems of migraineurs that influences reaction time (75). In the fMRI study discussed in chapter 2, significant increases in rCBF were also observed within the pons in CH patients,

encompassing locus coeruleus, thus possibly explaining the increased variability found in this study. Indeed, Andrea and colleagues postulated that CH may be due to a dysfunction of the noradrenergic system and reported efficacy of Clonidine, an alpha-2-adrenergic presynaptic agonist as a preventative treatment, even though a follow up study failed to confirm this finding (253, 254). A similar drug, Tizanidine has also been reported to have good efficacy in CH albeit that this was in an open-label study (255). There have also been reports of reduced levels of platelet adrenaline and noradrenaline in CH patients during remission, during the interictal period in a cluster bout and during an acute attack compared to controls (256). Hence, whilst there may be a functional deficit in the noradrenergic system in migraine, there may be impairment involving both the noradrenergic and dopaminergic systems in CH.

Studies in other disorders affecting the BG, such as Parkinson's disease and Huntington's disease have also shown similar changes in saccadic latencies, with increases in mean and/or variability (70, 71, 73, 257). The authors have suggested that the high variability in saccadic latency distribution in PD reflects heterogeneity of the disorder, suggesting that the extent of underlying pathology may affect different elements that controls saccadic eye movement, which influences the degree of variability seen (73). Likewise, the degree of impairment or neurotransmitter imbalance within the noradrenergic and dopaminergic systems in CH patients may also partly explain the high variability in saccadic latency distribution seen.

Apart from characterising the neurological function in CH patients, the findings from this study also demonstrate that saccadometry has the potential to be used as a diagnostic tool. The sensitivity and specificity analysis performed suggested that 81% of individuals could be correctly assigned a diagnosis of CH by saccadometry alone. However, it should be borne in mind that the clinical features of CH are relatively

stereotyped and thus the key to diagnosing them is a detailed and systematic patient history. Thus, whilst the use of saccadometry as a tool in conjunction with a detailed history may help with diagnosis, particularly of complex or atypical cases of CH, its use in isolation as a diagnostic tool is limited at this stage.

Similar to the neuroimaging study, the small number of patients in this study may be a limiting factor. However, this issue is partly overcome by the large number of saccadic trials performed per patient (200 each), thus allowing generation of a large dataset. Furthermore, the study sample was very heterogeneous, although comparison of saccadic distributions between ECH and CCH failed to show any significant differences. The male to female ratio of the sample was also disproportionate owing to the disorder having a predilection for males, although it has been reported that there are no known significant differences in saccades across gender (78). As reaction time can be influenced by external stimuli, the experimental conditions were ensured to be conducive to and consistent across patients, thus minimizing any possible confounding effects.

In conclusion, saccadometry is a non-invasive, quantitative discriminatory measure that is simple to perform (both for clinician and patient) and has proven to be a sensitive indicator of underlying neural impairments in CH patients. This study has found significant differences in the main distributions of saccadic latencies of CH patients, with reduction in early saccade generation. These abnormalities in saccadic reaction time distributions suggest neural impairment possibly involving both the noradrenergic and dopaminergic systems. However, any conclusions or functional interpretations regarding the structures or neural mechanisms that may explain the changes seen in saccadic reaction time distributions in this study must necessarily be very speculative at this stage.

Chapter 4 Development and validation of a CH specific quality of life scale

4.1 Introduction

In CH, assessment of HRQoL is currently limited to use of generic scales, such as the SF-36 (3, 4, 162, 258). Although generic instruments have the advantage of allowing comparisons with other medical conditions and healthy controls, they may not necessarily capture the specific burden of a headache disorder. Thus attempts have been made at adopting the migraine-specific HRQoL instruments for use in CH patients, since they share the same dominant symptom (headache). Ertsey and colleagues used the MSQ version 2.1 to assess HRQoL in ECH patients during and after their cluster bout (4). They found that, as expected, there was a highly significant difference in HRQoL between CH patients and controls; however, surprisingly, the difference between CH patients and migraineurs was not significant. Therefore, this raises the question of the sensitivity of using migraine-specific HRQoL scales in CH, particularly in light of the differences between the two disorders in terms of pain intensity and frequency (4). For this reason, the aim of this study was to develop and validate a new CH-specific HRQoL tool, which may better reflect the true nature of the impact of this highly disabling disorder on patients' daily life, as existing generic and migraine-specific HRQoL measures have failed to show specificity and sensitivity in capturing and highlighting the burden in this patient group (4, 162).

4.2 Methods

Ethical approval for this study was obtained from The North West London Research Ethics Committee. Informed written consent was obtained from all participants prior

to enrolment in the study. Data was collated in an electronic database and all statistical analyses were performed using SPSS software version 18. The steps employed in the development and validation of the scale have been described by Guyatt and colleagues and have been used in the development of other disease-specific HRQoL measures (90, 259, 260) A three-step approach was utilised; first item generation, second item reduction and scale development, and finally scale validation and reliability testing.

4.2.a Item generation

A comprehensive review of the literature was conducted and existing headache-specific HRQoL scales were studied to generate an overview of the areas of life impacted by CH. This was followed by an in-depth semi-structured interview of 24 CH patients (M:F 2.6:1, mean age 46.3 years), diagnosed according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD-II), who attended the headache clinic at The National Hospital for Neurology and Neurosurgery, London (7). The areas covered during the interview included pain characteristics, aspects of the patient's life that were affected by their headaches, their support system; both practical and emotional, and their outlook on life. These processes allowed generation of a preliminary questionnaire, which was then discussed with a panel of experts with an interest in headache. Any ambiguous or similar items were eliminated or grouped together, before a final set of items were agreed upon. A 54-item questionnaire was subsequently drafted, each with a range of five possible answers on a Likert scale: never, occasionally, sometimes, often and always, addressing areas of life impacted by CH within the past month. A visual analogue scale was added to the end of the questionnaire to rate overall satisfaction with life (0= extremely dissatisfied, 100= extremely satisfied). Subsequently, a pilot

study was conducted with 24 patients with CH to assess the face validity and clarity, and the questionnaire was then adjusted accordingly and reduced to 47-items.

4.2.b Item reduction and scale development

There were two sources of CH patients for this study: (i) Patients with a diagnosis of CH attending the headache clinic at The National Hospital for Neurology and Neurosurgery, London and (ii) an invitation letter to participate in the survey was posted out to CH patients via OUCH UK (The Organisation for the Understanding of Cluster Headache, United Kingdom). Those who responded to the invitation letter were contacted via telephone and had their headaches phenotyped. A booklet of questionnaires, which included the 47-item CH-QoL questionnaire was then given or posted out to all participants who satisfied the ICHD-II diagnostic criteria for CH (n=521). Details on demographics, headache history and characteristics were collected from the questionnaires. A number of other frequently utilised and previously validated generic or disease specific HRQoL instruments were also included in the booklet to allow assessment of convergent validity of this new scale, including the SF-36 Health Survey Questionnaire (SF-36), the EQ-5D Questionnaire and the Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1), the Migraine Disability Assessment Test (MIDAS) and the Headache Impact Test (HIT-6).

Standard procedures for item reduction were employed. The first step in item reduction involved removing items based on their inter-item correlations. This is common practice in scale development and is done to retain items with the best inter-item correlations, thus allows shortening of the instrument, whilst simultaneously improving homogeneity and reliability estimates (261-263). Items that showed low inter-item correlations ($r < 0.1$) were excluded as this demonstrated that they were poorly correlated with the underlying scale, thus were less likely to be measuring the

same construct as the rest of the scale. On the other hand, any items that showed high inter-item correlations ($r > 0.7$) were examined for content similarity. The least clinically sensible item was excluded, as theoretically, items that correlated too highly with each other implies that they are measuring the same underlying dimension (261, 264).

Next, an exploratory factor analysis was performed to determine the underlying key domains of the 47-item questionnaire. Since there was reason to believe that these domains would correlate with each other, oblique rotation was employed for the analysis. An eigenvalue cut off point >1 was used to extract underlying factors, and any items that loaded highly (above 0.4) on a factor was considered relevant.

4.2.c Scale validation and reliability testing

Convergent and divergent validity were assessed by measuring the Pearson's correlation of the underlying subscales of the CH-specific HRQoL questionnaire with the subscales of SF-36 and MSQ v2.1. Meanwhile, Spearman's correlation test was employed to assess validity of the questionnaire and the EQ-5D, due to the ordinal nature of the latter. Convergent and divergent validity are components of construct validity; providing a measure of the ability of the questionnaire to examine its intended constructs i.e. HRQoL in CH patients. Hence, convergent validity was assumed if there was a high correlation between subscales measuring the same construct, whilst divergent validity was assumed when there was low correlations on unrelated subscales.

Known-group validity was examined by assessing how the mean scores of the scale and its subscales were related to the various categories of MIDAS and HIT-6, by using one way ANOVA test followed by post hoc analysis with the total and subscale scores as dependent factors. This form of validation illustrates the ability of the

questionnaire to discriminate across groups. The MIDAS assesses disability in three domains, namely paid work or school, household and family, social or leisure activities. Headache sufferers are then categorized into four groups, depending on the frequency of disability in these domains due to their headaches; little or no disability, mild disability, moderate disability and severe disability. Similarly, the HIT-6 categorizes headache sufferers into four groups depending on the impact of their headache on the same domains, namely little or no impact, some impact, substantial impact and severe impact.

The internal consistency is a measure of reliability; specifically how well items in the questionnaire that are supposed to measure the same construct are in yielding consistent results. This was assessed by the Cronbach's coefficient alpha (α), with high values suggesting measurement of a single construct (103). Reliability can also be assessed by the item-test correlation of a subscale, which measures how well items within that subscale are in measuring its intended construct. The recommended criteria for good internal consistency is $\alpha > 0.70$ (265), whilst for item-test correlations values should be greater than 0.40 (266).

A same copy of the 47-item questionnaire was sent out to 75 randomly selected respondents two weeks after they first completed the questionnaire, to allow assessment of the test-retest reliability of the new scale, using two-way mixed, single measure intra class correlation coefficients (ICC 3,1). Two weeks was chosen as the follow-up period, as it was assumed that this would be long enough a lapse to avoid recalling of original responses without any significant changes in HRQoL.

4.3 Results

4.3.a Subjects

A total of 406 completed questionnaires were received, giving a response rate of 77.9%. From this total, 148 patients (36.5%) were recruited from the headache clinic and 258 patients (63.5%) were recruited through the patient organisation. About fifty-nine percent of the responders (239 patients) had ECH and 41.1% (167 patients) had CCH. The mean age of the study sample was 52.4 years (range 20.5 - 84.4). There were 68.2% males and 31.8% females, with a mean age of onset of CH of 33.0 years (range 8 - 69).

4.3.b Item reduction and generation of subscales

Eight items had low inter-item correlations of < 0.10, and were subsequently removed from the scale (Table 4.1).

Table 4-1 Items with low inter-item correlations

- Generally enjoyed the things that you do?
- Had to give up something that you enjoyed like alcohol or smoking?
- Felt happy or satisfied with your personal life?
- Had to be alone during a cluster headache episode?
- Been restless, could not sit still, paced up and down?
- Felt less sensitive to (or more tolerant of) pain?
- Felt stronger as a person as a result of coping with cluster headache?
- Contributed to household duties e.g. housework, cooking, etc?

Meanwhile, two pairs of items had correlations above 0.70; one pair was asking about work, whilst another was looking at prognosis. The items "felt unable to complete duties at work" and "felt that you were losing control over your health and over your own life" were retained as they were felt to be more clinically sensible.

The exploratory factor analysis produced five factors, consisting of 37 items, which explained 59.18% of the variance. One factor with an eigenvalue of 1.13 (explaining 3.05% of the variance) was removed as it only had one item (avoided potential headache triggers e.g. alcohol, bright lights, perfume, noise) loading onto it and therefore was considered insufficient to produce a meaningful subscale (267). The remaining factors and items were then examined to determine if there was any scope for further reduction of the number of items to produce a more meaningful and user-friendly scale. Eight items were omitted as they failed to gain significant loading (> 0.40) on any of the factors created (Table 4.2).

Table 4-2 Items removed due to poor factor loading

- Felt negative or pessimistic about the future?
- Had to rely on family and close friends for help?
- Experienced a general lack of motivation to do things?
- Felt that you were losing control over your health and over your own life?
- Felt depressed, sad or tearful?
- Felt frightened or worried about getting a headache in public?
- Felt less interested in sexual relations?
- Felt frustrated?

This resulted in a 28-item questionnaire CH-specific HRQoL scale (CHQ), which explained 56.14% of the variance (Table 4.3). The Cronbach's alpha was calculated

and compared for the factors prior to, and after removal of these items, to ensure that it did not compromise the internal consistency of the scale (265). Expert opinion was also sought throughout this process to ensure there was no removal of clinically relevant items.

Based on the results of the factor analysis, nine items were grouped onto a factor addressing various '*Restrictions of activities of daily living'* (ADL), such as avoiding leaving the house, making plans and inability to complete duties at work. Twelve items described *'Impact on mood and interpersonal relationships'*, such as feelings of being dismissed by others and worthlessness, including any suicidal tendencies. Two items loaded on a 'Pain and anxiety' factor that addressed the pain of the CH and any associated anxiety such as dreading that the headache not going away. Finally, a '*Lack of vitality'* (five items) factor addresses problems related to energy and cognition, for example difficulties in thinking clearly and concentration.

Table 4-3 Results of the principal component factor analysis of the scale

Items	Factor loadings/correlations			
	Factor 1 Restriction of ADL	Factor 2 Impact on mood and interpersonal relationships	Factor 3 Pain and anxiety	Factor 4 Lack of vitality
Avoided leaving the house	0.76			
Avoided making plans due to unpredictability of CH e.g. holidays	0.72			
Felt unable to complete duties at work	0.66			
Had difficulty in getting involved in leisure activities e.g. cinema, theatre, etc?	0.63			
Avoided crowded and noisy places e.g. public transport, pubs, etc	0.57			
Felt that the severity of cluster headache affected your daily activities	0.56			
Been less involved in family affairs e.g. interaction with children, planning holidays	0.54			
Been unable to socialise/spend time with friends and family	0.46			
Been unable to achieve your daily goals and carry out routines and chores	0.42			
Felt less respected by others		0.89		
Had problems with close personal relationship		0.73		
Felt you were a burden on family and friends		0.71		
Felt self-conscious and uncomfortable about your appearance after a cluster headache attack (eg swelling/redness of eyes and facial sweating, etc)		0.68		
Felt that others are dismissive of your cluster headaches		0.61		
Felt aggressive		0.53		
Felt bad about yourself, lost self-confidence or felt worthless		0.53		
Felt like harming yourself or suicidal		0.53		

Items	Factor loadings/correlations			
	Factor 1 Restriction of ADL	Factor 2 Impact on mood and interpersonal relationships	Factor 3 Pain and anxiety	Factor 4 Lack of vitality
Been irritable, impatient or less tolerant		0.53		
Been forgetful e.g. missed appointments		0.49		
Been unable to take care of your appearance (eg take a bath, put make-up on, change clothes etc)		0.49		
Felt isolated, lonely or vulnerable		0.45		
Found your pain is unbearable if untreated			0.67	
Dreaded that the headache would not go away			0.48	
Felt lacking in energy and constantly tired				-0.88
Felt sleepy, worn out or less able to concentrate due to nocturnal attacks of CH				-0.72
Had problems concentrating e.g. reading paper, watching TV, etc				-0.62
Been unable to think clearly				-0.60
Felt tense or anxious				-0.48
% of variance explained	43.11	5.59	4.06	3.38

ADL = activities of daily living, CH = cluster headache

4.3.c Construct validity

There was good intercorrelation between the subscales derived from the factor analysis, as shown in Table 4.4. This ranged from 0.52 – 0.75, supporting internal construct validity. Meanwhile, the subscales and total score had a moderate to strong negative correlation with the VAS. This negative correlation was expected as their scores ran in opposite direction (higher VAS indicates better HRQoL whereas higher total score indicates poorer HRQoL).

Table 4-4 Pearson's correlation coefficient between subscales

Subscale / Subscale	Restriction of ADL	Impact on mood and interpersonal relationships	Pain and anxiety	Lack of vitality	Total score	VAS
Restriction of ADL	1.00					
Impact on mood and interpersonal relationships	0.69*	1.00				
Pain and anxiety	0.52*	0.53*	1.00			
Lack of vitality	0.75*	0.69*	0.52*	1.00		
Total score	0.89*	0.93*	0.64*	0.85*	1.00	
VAS	-0.52*	-0.58*	-0.30*	-0.43*	-0.57*	1.00

ADL = activities of daily living; VAS = visual analogue scale
*correlation is significant at the 0.01 level

The scale was assessed for convergent and divergent validity by measuring correlation of the subscales with the relevant subscales of the SF-36, EQ-5D and MSQ (Table 4.5). With regards to the SF-36, the 'Restrictions of ADL' factor of the scale correlated significantly with the social role functioning (SF) (r = -0.47, p < 0.001), mental health (MH) (r = -0.51, p < 0.001) and emotional role functioning (RE) subscales (r = -0.41, p < 0.001). The 'Impact on mood and interpersonal relationships' subscale of the scale correlated with SF (r = -0.52, p < 0.001), RE (r = -0.50, p < 0.001), vitality (VT) (r = -0.49, p < 0.001) and MH (r = -0.67, p < 0.001) subscales. The 'Lack of vitality' subscale of the scale correlated with VT (r = -0.43, p < 0.001) and MH (r = -0.50, p < 0.001). All the correlations were negative as the scale and SF-36 were scored in different directions.

Meanwhile, all of the subscales correlated significantly with all of the EQ-5D domains with the correlations having small to moderate magnitudes, except for the pain and anxiety subscale of CHQ and the mobility domain of EQ-5D, thus supporting

convergent validity. The highest correlation observed was between the 'Impact on mood and interpersonal relationships' subscale of the scale and anxiety/depression item of the EQ-5D (r = 0.54, p < 0.001). In relation to the MSQ, the subscales correlated significantly with the role restrictive and emotional functioning domains. In particular, there was a good correlation between the 'Impact on mood and interpersonal relationships' subscale with the emotional functioning subscale of the MSQ (r = 0.65, p < 0.001). Furthermore, the total score of the scale and total MSQ scores were well correlated (r = 0.61, p < 0.001).

Table 4-5 Correlation coefficients between the subscales and the EQ-5D and SF-36 generic and MSQ v2.1 migraine-specific quality of life measures

	Restriction of ADL	Impacts on mood and interpersonal relationships	Pain and anxiety	Lack of vitality
EQ-5D				
Mobility	0.28**	0.27**	0.07	0.21**
Self-care	0.31**	0.39**	0.10*	0.27**
Usual activities	0.35**	0.43**	0.14**	0.29**
Pain/discomfort	0.19**	0.30**	0.11*	0.15**
Anxiety/depression	0.39**	0.54**	0.28**	0.38**
SF-36				
Physical functioning (PF)	-0.28**	-0.37**	-0.11*	-0.24**
Role physical (RP)	-0.23**	-0.32**	-0.05	-0.17**
Bodily pain (BP)	-0.23**	-0.31**	-0.12*	-0.22**
General health (GH)	-0.34**	-0.46**	-0.15**	-0.32**
Vitality (VT)	-0.37**	-0.49**	-0.22**	-0.43**
Social functioning (SF)	-0.47**	-0.52**	-0.21*	-0.43**
Role emotional (RE)	-0.41**	-0.50**	-0.21**	-0.39**
Mental health (MH)	-0.51**	-0.67**	-0.37**	-0.50**
MSQ v2.1				
Role restrictive (RR)	0.52**	0.53**	0.29**	0.45**
Role preventive (RP)	0.56**	0.52**	0.28**	0.42*
Emotional functioning (EF)	0.49**	0.65**	0.41**	0.47**

ADL = activities of daily living, EQ-5D = The European Quality of Life scale, SF-36 = Short Form 36-item Health Survey, MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire Version 2.1

Pearson's correlation test was used for SF-36 and MSQ v2.1 and Spearman's correlation test used for EQ-5D

** correlation is significant at the 0.01 level

* correlation is significant at the 0.05 level

4.3.d Known-group validity

The questionnaire was examined for known-group validity by assessing the relationship between the mean scores of the scale and its subscale with the MIDAS and HIT-6 groups.

i MIDAS

With regards to the MIDAS, there was a linear increase in mean total scores of the scale, indicating poorer HRQoL, with increasing disability grade (Table 4.6). The assumption of homogeneity of variance was violated, thus a Welch F test was conducted instead of the oneway ANOVA test. The difference was statistically significant as determined by this test (Table 4.7). Similarly, oneway ANOVA and Welch F tests demonstrated there were statistically significant differences between the disability groups in all but one of the subscales (pain and anxiety), thus post hoc analysis was not conducted on this subscale. Games-Howell post hoc comparisons revealed there were statistically significant differences ($p < 0.05$) between little/no and severe, as well as mild and severe disability groups in all subscales. There was also statistically significant difference ($p < 0.05$) between moderate and severe disability groups in the total and restriction of activities of daily living subscales. Meanwhile, there were no statistically significant differences between little/no and mild, little/no and moderate, as well as mild and moderate disability groups in all subscales.

ii HIT-6

The oneway ANOVA and Welch F tests demonstrated statistically significant differences between the four groups in all subscales as well as in the mean total score. Games-Howell post hoc comparisons revealed there was statistically significant difference ($p < 0.05$) between little/no and severe impact groups in all subscales. There were also statistically significant differences ($p < 0.05$) between some and severe, as well as substantial and severe impact groups in all subscales except for pain and anxiety. Differences were also seen between little/no and substantial impact group in impact on mood and interpersonal relationship subscale. There were no statistically

significant differences between little/no and some, as well as some and substantial impact groups in all subscales.

Table 4-6 Mean subscales and total scores across the MIDAS and HIT-6 groups

Mean score / Group	Restriction of ADL	Impacts on mood and interpersonal relationships	Pain and anxiety	Lack of vitality	Total
MIDAS					
Little or no disability	19.98	16.59	6.29	12.42	55.45
Mild disability	19.71	16.26	6.33	12.47	55.63
Moderate disability	20.18	20.69	6.1	14.18	62.0
Severe disability	25.45	25.32	6.78	15.0	72.87
HIT-6					
Little or no impact	18.07	10.41	5.19	10.0	43.0
Some impact	18.58	14.93	6.3	12.07	51.47
Substantial impact	20.0	17.76	6.07	12.74	56.19
Severe impact	24.69	24.45	6.81	14.91	71.47

ADL = activities of daily living, MIDAS = The Migraine Disability Scale, HIT-6 = The Headache Impact Test 6 items

Table 4-7 Oneway ANOVA and Welch F test results across the MIDAS and HIT-6 groups

	Restriction of ADL	Impact on mood and interpersonal relationships	Pain and anxiety	Lack of vitality	Total
MIDAS					
F-statistics	F (3,55) = 16.94	F (3,336) = 19.38	F (3,56) = 2.58	F (3,59) = 10.87	F (3,51) = 16.48
p value	< 0.001	< 0.001	0.062	< 0.001	< 0.001
HIT-6					
F-statistics	F (3,61) = 11.33	F (3,363) = 27.17	F (3, 66) = 7.07	F (3, 62) = 13.89	F (3,61) = 23.88
p value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

ANOVA = analysis of variance, MIDAS = The Migraine Disability Scale, HIT-6 = The Headache Impact Test 6 items, ADL = activities of daily living

4.3.e Internal consistency and reproducibility (Reliability)

The reliability estimates (Cronbach's coefficient alpha) and corrected item to total correlations of the items to their resulting subscale are shown in Table 4.8. The scale had a Cronbach's coefficent alpha (α) of 0.95, which was well above the recommended criteria of 0.70. Meanwhile, the α values for the subscales ranged from 0.52 – 0.91, with the pain and anxiety subscale not reaching the benchmark. The item-test correlations of the subscales ranged from 0.37 – 0.78, thus most were above the recommended criteria of 0.40, except for the two items under the pain and anxiety subscale. There was no effect on α if any item were deleted from the subscales, thus all items were retained in their respective subscales.

Table 4-8 Item to total correlations and Cronbach's coefficient alpha for the scale

Subscale/Items	Corrected item to total correlation	Cronbach's alpha
Restriction of ADL		0.91
Avoided leaving the house	0.67	
Avoided making plans due to unpredictability of CH e.g. holidays	0.66	
Felt unable to complete duties at work	0.70	
Had difficulty in getting involved in leisure activities e.g. cinema, theatre, etc?	0.78	
Avoided crowded and noisy places e.g. public transport, pubs, etc	0.63	
Felt that the severity of cluster headache affected your daily activities	0.68	
Been less involved in family affairs e.g. interaction with children, planning holidays	0.67	
Been unable to socialise/spend time with friends and family	0.73	
Been unable to achieve your daily goals and carry out routines and chores	0.69	
Impact on mood and interpersonal relationships		0.90
Felt less respected by others	0.72	
Had problems with close personal relationship	0.71	
Felt you were a burden on family and friends	0.73	
Felt self-conscious and uncomfortable about your appearance after a cluster headache attack (eg swelling/redness of eyes and facial sweating,etc)	0.65	
Felt that others are dismissive of your cluster headaches	0.50	
Felt aggressive	0.59	
Felt bad about yourself, lost self-confidence or felt worthless	0.63	
Felt like harming yourself or suicidal	0.59	
Been irritable, impatient or less tolerant	0.63	
Been forgetful e.g. missed appointments	0.58	
Been unable to take care of your appearance (eg take a bath,put make-up on,change clothes etc)	0.55	
Felt isolated, lonely or vulnerable	0.71	
Pain and anxiety		0.52
Found your pain is unbearable if untreated	0.37	
Dreaded that the headache would not go away	0.37	
Lack of vitality		0.85
Felt lacking in energy and constantly tired	0.69	

Subscale/Items	Corrected item to total correlation	Cronbach's alpha
Felt sleepy, worn out or less able to concentrate due to nocturnal attacks of CH	0.61	
Had problems concentrating e.g. reading paper,watching TV,etc	0.64	
Been unable to think clearly	0.70	
Felt tense or anxious	0.66	

ADL = activities of dailiy living, CH = cluster headache

Fifty-six completed questionnaires were received (71.7% response rate) for the assessment of test-retest reliability. The mean age of this subsample was 55.7 years (range 34.7-79.1). There were 66.1% males and 33.9% females, with a mean age of onset of CH of 36.4 years (range 12.0-66.0). Test-retest reliability testing of the scale was performed on the data collected from respondents who completed the questionnaire on two occasions, which showed significant correlation coefficients between the two assessment occasions. Two-way mixed, single measure intra class correlation coefficient (ICC 3,1) was 0.87. The intra class coefficients for the subscales ranged from 0.71 – 0.84. Cronbach's alpha was also satisfactory for the scales on both occasions (Table 4.9).

Table 4-9 Cronbach's coefficient alpha and test-retest reliability at the first and second assessments

Scale	Cronbach's alpha time 1	Cronbach's alpha time 2	Test-retest reliability
Restriction of ADL	0.91	0.93	0.85 $p < 0.001$
Impact on mood and interpersonal relationships	0.90	0.87	0.83 $p < 0.001$
Pain and anxiety	0.52	0.63	0.71 $p < 0.001$
Lack of vitality	0.85	0.80	0.80 $p < 0.001$

ADL = activities of daily living

4.4 Discussion

Several studies have demonstrated that HRQoL is significantly impaired in patients with CH (3, 4, 161-164). However, these studies have all used either generic HRQoL scales such as the SF-36, or migraine-specific scales that may not necessarily be able to capture the true effects of CH, and may therefore be underestimating the actual impact of the disorder on HRQoL. Indeed, some issues that are specific to CH are not addressed through the use of these scales, for example suicidal tendencies, which is prevalent among CH sufferers. Circadian periodicity is another distinct feature in this disorder, with patients usually being woken up around the same time every night, at the onset of rapid eye movement (REM) sleep, which can have a major impact on patients with CH and therefore should be addressed and included in HRQoL assessments in this patient group.

In the current study, a CH-specific HRQoL scale, the CHQ, was developed and validated. Items for the scale were generated from an in-depth literature review and semi-structured patient interviews, allowing CH sufferers to express their views about the various aspects of their lives that they felt were affected by the disorder and should be highlighted in such a disease specific HRQoL scale. This was followed by a review by a panel of experts with an interest in headaches to include items that were considered clinically relevant. These steps allowed development of a scale that is based on both patient and clinician input, thus ensuring good content and face validity. Exploratory factor analysis yielded five factors that explained 59.18% of the variance. However, since the fifth factor only had a single item loading on it, it was considered insufficient to produce a meaningful subscale and was consequently removed (267). A further eight items were subsequently removed as they failed to load significantly (> 0.40) on any factor.

Thus, four subscales explained the resultant CH-specific HRQoL scale, namely restriction of activities of daily living (nine items), impact on moods and interpersonal relationships (12 items), pain and anxiety (two items) and lack of vitality (five items) subscales. These were shown to have good intercorrelations (range 0.52 – 0.75), supporting good construct validity. In terms of convergent validity, the subscale scores showed good correlation with those of other widely used HRQoL scales that have already been shown to have good validity and reliability, specifically the SF-36, EQ-5D and MSQ. Although some of the CHQ subscales did show weak correlation ($r < 0.30$) with the other HRQoL subscales, this was not surprising as the actual contents of these subscales may be different across the questionnaires used, despite them having similar titles or themes (268).

Known group validity was assessed based on the mean total and subscales scores of the CH-specific HRQoL scale in the MIDAS and HIT-6 groups. In terms of the MIDAS, there was a statistically significant difference in mean total scores between the disability groups, with the severely disabled having significantly higher scores compared to the others. This suggests that greater headache-related disability is associated with poorer HRQoL in CH patients, with the impact being most evident in the severe disability group. The same pattern was seen with the restriction of activities of daily living subscale, since the MIDAS is effectively a measure of headache impact on daily function, thus they are measuring the same construct. This correlation supports convergent validity of this subscale. On the other hand, the change in the mean scores of the pain and anxiety subscale was not significant between the four disability groups. This may be because the pain of each CH attack is almost always excruciating that it is unaffected by any associated headache-related disability.

With regards to the HIT-6, there were statistically significant differences in mean total and subscale scores between the four impact groups. The change in mean scores of total and subscales were greatest between the little/no, some or substantial and the severely impacted groups, except for pain and anxiety subscale. HIT-6 is a measure of the functional impact of headaches, thus it is not surprising that those who are severely impacted also have significantly poorer HRQoL. Since HIT-6 also includes items such as feeling too tired and feeling fed up or irritated because of headaches, the changes in mean scores were also seen in the impact on moods and interpersonal relationships and lack of vitality subscales, reflecting good convergent validity. Moreover, the fact that there were significant changes in the mean total score of the scale between the four different groups of the MIDAS and HIT-6 scales also demonstrates that it has good discriminative property in respect to the magnitude or severity of associated disability.

The Cronbach's coefficient alpha for the scale was 0.95, which was well above the recommended criteria. This indicates that all items in this scale are measuring the same construct, specifically HRQoL. The subscales also had high α values, in the range of 0.85 – 0.91, with the exception of pain and anxiety subscale that had α value of 0.52. This may be due to the fact that this subscale only consisted of two items, with one measuring pain (found your pain is unbearable if untreated) and the other assessing anxiety (dreaded that the headache would not go away). Thus the variability in the contents of this subscale is likely to account for this low internal consistency. Although there was an item on anxiety (felt tense or anxious) in the lack of vitality subscale, this item had poor loading (0.059) on the pain and anxiety subscale. Furthermore, this item had very good item-total correlation in its existing subscale

(0.66) and would actually reduce the internal consistency of the subscale if deleted. Thus this item was retained in the lack of vitality subscale.

A second copy of the same questionnaire was completed by a random sample of respondents two weeks later to assess its test-retest reliability. This time period was similar to that employed in the migraine-specific quality of life measure (MSQOL) development and validation study (99). Intra class correlation coefficients ranged from 0.71 – 0.84, which is considered acceptable and suggests good intra rater reliability across time. Moreover, the Cronbach's coefficient alpha ranged from 0.63 - 0.93 on the second assessment, indicating that the scale has good consistency with time.

A limitation of the quality of life study was that about a third of the study population comprised patients attending a tertiary referral centre; hence medically intractable cases might be over-represented in this sample. Of the 148 patients recruited from the headache clinic, 64.2% had CCH, which is significantly greater than is expected in the general population (8). Thus this sample may not be totally representative of the CH population in the community. However, this bias enabled data to be collected from a fair proportion of CCH sufferers (41.1%), who due to the recurring nature of their headaches are likely to be more disabled by this disorder, giving us a better picture of the extent of the impact on patients quality of life. There may also be response bias as the CH-specific HRQoL was sent out together with the other scales in the same booklet, thus all questionnaires might have been completed simultaneously. However, previous studies using the same measures, for example, the SF-36 Health Survey have shown similar levels of impairment as our sample population.

To the best of my knowledge, this is the first scale developed to objectively measure HRQoL specifically in patients with CH. Following administration to a large sample of patients with the disorder, the scale has been shown to have good construct validity,

discriminative property, internal consistency and test-retest reliability. The scale was intended to be brief and user-friendly (it takes about 10 minutes to complete the questionnaire) so that it can be used in the clinical setting as well as in clinical trials as a patient-reported outcome measure.

Chapter 5 Quality of life in cluster headache

5.1 Introduction

Quality of life studies in patients with CH have shown limitations in normal daily functioning as well as social functioning (3, 162, 166). The excruciating nature of CH attacks, which are considered to be worse than migraine, correlated with marked limitations in role and emotional functioning, with studies showing a high prevalence of depressive symptoms and suicidal tendencies in CH patients (3, 4, 161, 164). More than 70% of patients have reported that they have been severely impacted by their headaches, with restrictions in various life domains including paid work, household duties, social, leisure and family activities (164). This impairment continues even outside of the cluster bout, with considerable impact on social and family life, having to frequently miss social events and family gatherings. In terms of paid work, CH has led to reduced ability to work, limitations in career, loss of jobs and early retirement (161, 163). Due to their disability, CH patients have also had to depend highly on family and friends for help and support. Thus it is not surprising that almost all of the CH patients in a previous study reported having had to make some form of lifestyle change due to the disorder (163). It is therefore striking that the effect of CH on HRQoL in these studies were less marked, though this should be treated with caution, as their sample sizes were small. Furthermore, there were no significant differences found in the HRQoL between ECH patients during a bout and CCH patients (161, 162), which was not expected considering the lack of remission in the latter. This study is therefore set out to describe the sociodemographic and headache characteristics of a large cohort of CH patients and specifically to assess their HRQoL,

in particular trying to identify any differences between ECH and CCH patients in terms of their reported HRQoL.

5.2 Methods

5.2.a Subjects

Data were collected as part of the CH-specific HRQoL scale development and validation study. Four hundred and six patients with CH who were recruited and responded to the postal questionnaire were involved. Patients received a range of other measures within the booklet of questionnaires that they received as part of the scale development study, including HRQoL instruments, headache-specific HRQoL and disability scales, social support instrument and measures of psychological health.

5.2.b Questionnaires included in booklet

i Demographics

Demographic data on age, gender, marital status, employment status, current occupation or job done for the longest period and years of education were collected using a custom-made questionnaire. Data on smoking status was also collected as it is well known that a high percentage of CH sufferers engage in this habit.

ii Headache characteristics

Headache history including age of onset of CH, information on when the current bout started or last bout was, length of remission period, laterality and location of CH attacks, pain severity, frequency and duration, associated cranial autonomic symptoms, associated nausea or vomiting, existence of warning symptoms prior to attacks and any coexisting headache disorders were also evaluated as part of the custom-made questionnaire. Remission period over the past year was assessed as

either having no remission or remission lasting less than or more than one month. The side of CH attacks can be either strictly right-sided or left-sided, side shifting between attacks or bilateral. Pain severity was assessed using a five-point scale, ranging from mild, moderate, severe, very severe to excruciating. Participants had to indicate what cranial autonomic symptoms they experienced with their attacks, with available options including redness or watering of the eye, runny or blocked nose, drooping of eyelid, small pupil, swelling of eye, facial redness or sweating or ear discomfort. There was also a tick box for associated agitation or restlessness. If they had any warning symptoms before an attack, they were required to state what the warning symptom was and how long it lasted for.

In addition, participants were asked if they were any relieving factors for their pain and their current abortive and preventive medications. They were also queried on the year their CH diagnosis was made, who made the diagnosis and the number of doctors they saw before a CH diagnosis was made. Furthermore, their opinion regarding satisfaction with current treatment, their GP and OUCH were also assessed.

- Are you satisfied with your current treatment?
- Do you feel your GP is knowledgeable about your condition?
- Do you feel your GP appreciates how painful your CH can be?
- Do you think OUCH provided adequate information about CH?
- Do you think OUCH provided adequate support for you?

A ten-point scale was included to evaluate how much CH has changed their life in general, with one being least affected and ten being most affected, followed by a ten-

point scale assessing how much they have been affected in social (such as friends), professional (such as work) and private (such as family) domains.

iii Generic HRQoL instruments

The EQ-5D and SF-36 Health Survey were utilized to evaluate the influence of the headache in general on HRQoL.

The EQ-5D and SF-36 Health Survey were used to assess the impact of their CH on HRQoL in general. The EQ-5D has five domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three possible response options; no problems, some or moderate problems or extreme problems. In addition, there is a visual analogue scale, with 0 being the worst imaginable and 100 being the best imaginable current health state (96).

The SF-36 Health Survey contains 36 self-administered items, measuring functions in eight domains, namely physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social role functioning (SF), emotional role functioning (EF) and mental health (MH). The subscales are scored on a scale of 0 to 100, with higher scores indicating better HRQoL (94).

iv Headache-specific HRQoL instrument

The Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) was utilized to examine the impact of CH specifically on HRQoL since a measure for CH was not available. This is a 14-item measure, divided across three domains; role restrictive, role preventive and emotional functioning, which has been shown to have good internal consistency and construct validity (101). The total possible score ranges from 14 to 84, with higher scores indicating poorer HRQoL.

v Headache-specific disability instruments

Measures of disability provide an alternative method of assessing the impact of a disorder, and an inverse relationship between disability levels and HRQoL have been described (108). The instruments used to measure the degree of headache-related disability in this study were the Migraine Disability Assessment (MIDAS), the Headache Impact Test (HIT-6) and the Henry Ford Disability Inventory (HDI) questionnaires.

The MIDAS measures the number of days of disability due to headaches within the past three months, in terms of missed days and reduced productivity by 50% or more in various aspects of daily living. The areas covered are paid work or schoolwork, household duties and social, leisure or family activities. Scores are categorized into four disability grades; little or no disability (0-5 days), mild (6-10), moderate (11-20) and severe (>21) disability (269).

The HIT-6 is a six-item questionnaire used to measure the adverse impact of headaches in various domains; role and social functioning, cognitive functioning, vitality and psychological distress, as well as an item on pain severity. The scores range from 36 to 78, and functional impact due to headaches can then be categorized into four groups; little or no impact (< 49), some impact (50 – 55), substantial impact (56 – 59) and severe impact (60 – 78) (270).

The HDI is a 25-item questionnaire, divided into emotional and functional subscales, which is used to quantify the impact of headache on daily living, with higher scores reflecting greater disability caused by their headache (271).

vi Measures of psychological health

Previous studies have shown that there is a high prevalence of psychiatric comorbidity in headache sufferers. Thus in order to capture this effect in this sample of CH patients, a number of psychological health-related measures were utilized, including the HADS, the Starkstein Apathy scale (AS), the Beck Hopelessness Scale (BHS) and the General Health Questionnaire (GHQ-28).

The HADS is a widely used measure of anxiety and depressive symptomatology, consisting of seven items measuring anxiety alternating with seven depressive items. These were scored separately and scores of ≥ 8 defined anxiety and depression respectively (272). The Apathy scale (AS) has 14 items for screening and assessing the degree of apathy, with possible scores ranging from 0 to 42, and a cut-off score of 14 defining presence of low and high apathy (273). The BHS provides a measure of hopelessness or pessimism about the future. It consists of twenty items scored either true or false, thus having a possible total score ranging from 0 to 20, with higher scores reflecting greater hopelessness. Based on the scores, three levels of hopelessness can be ascertained; normal (0 – 3), mild hopelessness (4 – 8), moderate hopelessness (9 – 14) and severe hopelessness (15 – 20) (274). The GHQ-28 is a 28-item self-report measure of the common symptoms of mental health, specifically anxiety, depression, social withdrawal and somatic symptoms, which is used to screen for those who are at risk of or likely to have psychiatric disorders. The items are scored using a binary scoring method, with the first two available response options having a score of 0 and the last two responses having a score of 1. The total possible score ranges from 0 to 28, with scores ≥ 4 indicating psychiatric caseness (275).

vii Other instruments used

Two measures related to pain were included in the booklet of questionnaires, namely the McGill Pain Questionnaire (MPQ) and the Pain Behaviour Checklist (PBC). The MPQ is a measure of the subjective pain experience that includes 78 item describing quality of pain, divided across four domains, namely sensory, affective, evaluative and miscellaneous aspects of pain. The scores can be treated statistically and the total possible score ranges from 0 to 78, with higher scores indicating worse pain (203). The PBC is a 54-item scale that has been validated to measure the behavioural response of chronic pain patients. It is divided across three domains; help-seeking, avoidance and complaint behaviour (276).

The Rosenberg Self-Esteem Scale (RSES) is a widely used measure of self-esteem that includes both positive and negative feelings about ones' self. The questionnaire consists of ten items, each with a 4-point Likert response scale. Five items measure self-deprecation and another five assesses positive self-esteem, with lower scores indicating lower self-esteem (277).

The practical and emotional support system available to the participants was assessed using The Short Social Support Questionnaire, whereby they had to list down their sources of support, such as family or friends and rate their level of satisfaction with the support received on a 6-point scale, with 1 being very dissatisfied and 6 being very satisfied (modified from Jahanshahi and Marsden (278) and Sarason and colleagues (279)).

The level of participants' acceptance of and ability to adjust to their CH was measured using the Acceptance of Illness scale. This is an 8-item questionnaire describing the negative feelings associated with chronic disorders, with higher scores reflecting greater acceptance and better adjustment to their headaches (280).

Meanwhile, to assess the influence of stigma due to their CH, the stigma scale was included in the booklet of questionnaires. This contains six items, scored from 0 to 3, which assesses how their headache affects their interaction with others, such as avoidance behaviour, feelings of self-consciousness, unattractiveness and being different compared to others. A total score greater than 12 suggests severe stigma (281).

5.2.c Analysis

Data was collated in an electronic database and all statistical analyses were performed using SPSS software version 18. Mean, median, standard deviation and range or number and percentage values are presented for the sociodemographic and headache characteristics. Comparisons between these characteristics were performed using two-sample *t*-tests for continuous variables and Chi-square tests for categorical variables. A Shapiro-Wilk test was performed to test for normality of the data and appropriate parametric and non-parametric tests were applied accordingly to make comparisons between groups. Statistical tests were considered significant if $p < 0.05$.

5.3 Results

5.3.a Demographics

The sociodemographic characteristics of the study sample are presented in Table 5.1. About fifty-nine percent of the participants had ECH and 41.1% had CCH. The mean age ± SD of the study sample was 52.4 ± 12.3 years (range 21 – 84 years). There were 68.2% males and 31.8% females, with no significant differences in gender ratio between ECH and CCH participants. The groups differed in their employment status, with a greater percentage of CCH participants being unemployed (34.5% vs 5.1%, $p < 0.001$), whereby a high proportion was due to their disability. Occupation classes were

categorized according to the National Statistics Socio-economic Classification (NS-SEC) of higher occupation, intermediate occupation and lower occupation. There were significant differences between ECH and CCH patients in their occupation class, with more ECH patients having higher occupation compared to CCH patients (55.4% vs 39.1%, $p = 0.009$). There were no significant differences between groups in marital or smoking status and years of education, with > 65% having at least secondary level education.

Table 5-1 Sociodemographic characteristics of participants

Characteristic	Total (n = 406)	ECH (n = 239)	CCH (n = 167)	p values[1]
Age, mean ± SD (range)	52.4 ± 12.3 (21 – 84)	52.7 ± 12.7 (23 – 84)	52.0 ± 11.9 (21 – 84)	0.607
Gender (male: female)	2.1: 1	2.1: 1	2.3: 1	0.655
Marital status, n (%)				0.364
Single	60 (14.9%)	32 (13.5%)	28 (16.8%)	
Married/cohabiting	304 (75.2%)	184 (77.6%)	120 (71.9%)	
Widowed	12 (3.0%)	8 (3.4%)	4 (2.4%)	
Divorced/separated	28 (6.9%)	13 (5.5%)	15 (9.0%)	
Employment status, n (%)				< 0.001
Employed	228 (56.9%)	159 (67.4%)	69 (41.8%)	
Retired	85 (21.2%)	55 (23.3%)	30 (18.2%)	
Unemployed	69 (17.2%)	12 (5.1%)	57 (34.5%)	
Due to disability > 6 months	61 (15.2%)	8 (3.4%)	53 (32.1%)	
Never employed	19 (4.7%)	10 (4.2%)	9 (5.5%)	
Occupation class, n (%)				0.009
Higher occupation	191 (48.7%)	128 (55.4%)	63 (39.1%)	
Intermediate occupation	68 (17.3%)	39 (16.9%)	29 (18.0%)	
Lower occupation	122 (31.1%)	59 (25.5%)	63 (39.1%)	
Never employed	11 (2.8%)	5 (2.2%)	6 (3.7%)	
Years of education, n (%)				0.104
1 – 11	109 (27.4%)	57 (24.2%)	52 (32.1%)	
12 – 13	73 (18.3%)	39 (16.5%)	34 (21.0%)	
14 – 17	167 (42.0%)	107 (45.3%)	60 (37.0%)	
18 +	49 (12.3%)	33 (14.0%)	16 (9.9%)	
Smokers, n (%)	186 (45.8%)	105 (43.9%)	81 (48.5%)	0.363

ECH = episodic cluster headache, CCH = chronic cluster headache, SD = standard deviation

[1]Based on two-sample t-tests for continuous variables and Chi-square tests for categorical variables

The results of comparison of the sociodemographic characteristics with the CH-specific HRQoL questionnaire are shown in Table 5.2. Patients' current age were binned into three groups, specifically patients < 45 years old, between 46 and 59 years old and > 60 years old. There were significant differences in mean total HRQoL between the three age groups, with younger patients having poorer HRQoL. No significant differences were found in mean total HRQoL scores between males and

females (64.0 ± 21.2 vs 68.4 ± 21.7, p = 0.078). Oneway ANOVA test showed that there was a significant difference in mean scores within the marital status groups, with Hochberg GT2 post hoc comparison test showing that the difference was highly significant between the single and widowed groups. There were also significant differences in HRQoL scores according to employment status and occupation class, with the unemployed group being greatly affected in the former, whilst in the latter, the greatest difference in HRQoL was between the higher and lower occupation classes. No meaningful differences were found based on the years of education of the CH patients in this study.

Table 5-2 Comparison of CH-specific HRQoL scores and sociodemographic characteristics

Characteristic	Total HRQoL score		*p* values[1]
	Mean	SD	
Current age			< 0.001
< 45 years	73.3	18.5	
46 – 59 years	65.2	20.3	
> 60 years	55.6	22.7	
Gender			0.078
Male	64.0	21.2	
Female	68.4	21.7	
Marital status			0.008
Single	71.5	19.9	
Married/cohabiting	64.0	21.5	
Widowed	51.3	21.2	
Divorced/separated	71.6	20.1	
Employment status			< 0.001
Employed	64.7	20.6	
Retired	58.0	21.6	
Unemployed	77.8	17.1	
Never employed	59.2	27.7	
Occupation class			0.007
Higher occupation	61.5	22.1	
Intermediate occupation	66.6	17.4	
Lower occupation	70.3	21.5	
Never employed	70.8	21.0	
Years of education			0.889
1 -11	66.1	23.3	
12 - 13	66.7	20.9	
14 - 17	64.4	20.5	
18 +	65.4	21.6	

SD = standard deviation, CH = cluster headache, HRQoL = health related quality of life

[1]Based on two-sample *t*-tests and oneway ANOVA and Welch F tests

5.3.b Headache characteristics

The mean age of onset of CH of the whole study sample was 33.0 ± 13.0 years (range 8 – 69 years). Participants with CCH had a significantly later age of onset of their headaches compared to the ECH group (mean ± SD, 35.0 ± 12.8 vs 31.5 ± 13.2 years, p = 0.007), as shown in Table 5.3. The pain was strictly unilateral in 86.6% of patients, with right-sided attacks being commoner than the left. Attacks were side

variable in 9.6% of patients, while 15 patients (3.7%) had pain occurring on both sides during the same attack. The median duration of attack was 25.0 minutes, however two patients reported that their untreated attacks lasted seven hours. The majority (> 70%) of patients described the intensity of their headaches as excruciating. There were no meaningful differences in the number of attacks per day between ECH and CCH patients.

Table 5-3 Headache characteristics of participants

Characteristic	Total (n = 406)	ECH (n = 239)	CCH (n = 167)	p values[1]
Age at onset, mean ± SD (range)	33.0 ± 13.0 (8 – 69)	31.5 ± 13.2 (9 – 64)	35.0 ± 12.8 (8 – 69)	0.007
Remission period[2], n (%)				< 0.001
No remission	143 (35.8%)	-	131 (78.9%)	
< 1 month	50 (11.8%)	-	35 (21.1%)	
> 1 month	207 (52.5%)	239 (100.0%)	-	
Side of cluster headache, n (%)				0.045
Right	205 (50.6%)	129 (54.0%)	76 (45.8%)	
Left	146 (36.0%)	87 (36.4%)	59 (35.5%)	
Alternating	39 (9.6%)	18 (7.5%)	21 (12.7%)	
Bilateral	15 (3.7%)	5 (2.1%)	10 (6.0%)	
Duration in minutes, median (range)	25.0 (1 – 420)	22.5 (1 – 420)	25.0 (5 – 420)	0.078
Severity, n (%)				0.067
Mild	1 (0.2%)	-	1 (0.6%)	
Moderate	15 (3.7%)	4 (1.7%)	11 (6.6%)	
Severe	29 (7.1%)	18 (7.5%)	11 (6.6%)	
Very severe	61 (15.0%)	34 (14.2%)	27 (16.2%)	
Excruciating	300 (73.9%)	183 (76.6%)	117 (70.1%)	
Daily frequency, median (range)	3.0 (1.0 – 14)	3.0 (0.3 – 14)	3.0 (0.1 – 14)	0.786

ECH = episodic cluster headache, CCH = chronic cluster headache, SD = standard deviation

[1]Based on two-sample t-tests and Independent Samples Mann-Whitney U test for continuous variables and Chi-square tests for categorical variables

[2]Duration of remission period without medications on board

Headaches were focused mainly in the orbital, supra-orbital, temporal and frontal regions, although half of the study sample also experienced pain in the maxillary and mandibular distributions of the trigeminal nerve (Table 5.4). As per the diagnostic criteria for CH, many patients in this sample reported having associated cranial autonomic features, the most frequent being lacrimation, eyelid ptosis and conjunctival injection (Table 5.5). Patients with CCH reported a significantly greater occurrence of facial sweating, facial redness and ear discomfort compared to their episodic counterparts. A substantial proportion of patients (88.7%) also reported feeling restless or agitated with the headaches, while a third had associated gastrointestinal symptoms, specifically nausea or vomiting.

Table 5-4 Location of pain in cluster headache patients

Location	Total (*n* = 406)	ECH (*n* = 239)	CCH (*n* = 167)
Orbital	248 (61.1)	142 (59.4)	106 (63.5)
Supra-orbital	263 (64.8)	152 (63.6)	111 (66.5)
Frontal	154 (37.9)	82 (34.3)	62 (37.1)
Temporal	296 (72.9)	181 (75.7)	115 (68.9)
Parietal	128 (31.5)	74 (30.9)	54 (32.3)
Occipital	64 (15.8)	33 (13.9)	31 (18.6)
V_2/V_3	203 (50.0)	118 (49.4)	85 (50.9)
Ear	32 (7.9)	18 (7.5)	14 (8.3)
Neck	43 (10.6)	25 (10.4)	18 (10.8)

ECH = episodic cluster headache, CCH = chronic cluster headache, V_2/V_3 = second and third divisions of the trigeminal nerve
Results are presented as number of patients (percentage)

Table 5-5 Associated signs and symptoms with cluster headache attacks

Signs or symptoms	Total (*n* = 406)	ECH (*n* = 239)	CCH (*n* = 167)
Lacrimation	355 (87.4)	208 (87.0)	147 (88.0)
Eyelid ptosis	292 (71.9)	177 (74.1)	115 (68.9)
Conjunctival injection	276 (68.0)	159 (66.5)	117 (70.1)
Rhinorrhoea	267 (65.8)	159 (66.5)	108 (64.7)
Nasal congestion	219 (53.9)	130 (54.4)	89 (53.2)
Facial sweating	203 (50.1)	104 (43.5)*	99 (59.3)*
Eyelid swelling	142 (35.0)	92 (38.5)	50 (29.9)
Facial redness	136 (33.6)	69 (28.9)*	67 (40.1)*
Nausea or vomiting	134 (33.2)	82 (34.3)	52 (31.1)
Ear discomfort	122 (30.0)	60 (25.1)*	62 (37.1)*
Miosis	91 (22.4)	58 (24.3)	33 (19.8)
Agitation or restlessness	360 (88.7)	210 (87.9)	150 (89.8)

ECH = episodic cluster headache, CCH = chronic cluster headache
Results are presented as number of patients (percentage)
*Statistically significant difference between ECH and CCH, $p < 0.05$

More than half of the patients had a warning symptom before the onset of their CH (57.5%), which was usually within 10 – 30 minutes prior to an attack, although a small proportion of ECH patients reported having symptoms up to a month before. Amongst the symptoms reported were feelings of a dull ache or mild pain, feeling tired, irritable or nonspecifically unwell, stiffness or soreness particularly of the neck, onset of cranial autonomic symptoms or restlessness, paraesthesia or allodynia, feeling hot or sweaty, yawning and migraine-related features such as photophobia, phonophobia or nausea.

Almost a third of the patients in this sample (30.7%) suffered from another form of headache, the most common being migraine. Other types of headache reported were tension-type headache (nine patients), SUNCT (three patients) and short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA) (two patients).

Meanwhile three patients reported having primary stabbing headache, new daily persistent headache and Bechet-related headache respectively.

Relieving factors that can improve the pain or shorten the CH episode were reported by 35.4% of patients. This includes applying pressure or massage, particularly of the eye and neck, applying either hot or cold compresses such as ice packs, having a bath or shower, cooling down by having some fresh air or being in an air-conditioned room, having a caffeine drink such as coffee or Red Bull, banging the head against the wall or floor, pulling the hair, keeping busy and distracting ones' self from the pain and being in a dark room.

In terms of medications, more than half of the study sample used subcutaneous Sumatriptan and high dose and high flow oxygen as abortives. Other types of abortives used included Sumatriptan nasal spray, Zolmitriptan nasal spray, oral triptans, Lidocaine drops, non-steroidal anti-inflammatory drugs (NSAID) and opioids. Meanwhile, Verapamil was the commonly used preventive medication.

Most patients had their diagnosis of CH made by neurologists and headache specialists. This was more so for CCH patients (82.7% vs 58.2%, $p < 0.001$), whilst GPs were more comfortable in diagnosing ECH (34.5% vs 14.2%, $p < 0.001$). Other specialists seen for diagnosis were ENT doctors and dentists. An average of 3.8 doctors was seen before a definitive diagnosis was made, with the median duration to diagnosis being 4.3 years (range 0 – 46 years). Patients with ECH had a longer diagnostic delay compared to CCH patients (5.0 vs 3.0 years, $p = 0.018$).

Patients' satisfaction with their current treatment, their GP and OUCH is shown in Table 5.6. With regards to satisfaction with current treatment, about three-quarters of patients reported being satisfied (77.4%). About 45% of patients feel their GP are knowledgeable and appreciates how painful CH can be. The majority thought that

OUCH provided adequate information about the disorder; with significantly more ECH patients reporting that OUCH provided adequate support (88.7% vs 79.7%, p = 0.018) compared to CCH patients.

Table 5-6 Satisfaction of cluster headache patients with their treatment, their GP and OUCH

Domain	Total (n = 406)	ECH (n = 239)	CCH (n = 167)	p values[1]
Current treatment	298 (77.4)	185 (80.8)	113 (72.4)	0.054
GP:				
knowledgeable	176 (44.6)	108 (46.6)	68 (41.7)	0.341
appreciative	196 (49.4)	120 (51.3)	76 (46.6)	0.361
OUCH:				
adequate information	366 (93.6)	220 (95.2)	146 (91.3)	0.113
adequate support	307 (85.0)	189 (88.7)	118 (79.7)	0.018

ECH = episodic cluster headache, CCH = chronic cluster headache, GP = general practitioner, OUCH = Organisation for the Understanding of Cluster Headache
[1]Based on Chi-square tests for categorical variables
Results are presented as number of patients (percentage)

Cluster headache has a significant impact on patients' lives, with CCH patients reporting a greater impact than ECH patients (median score 10 vs 8, $p < 0.001$). This impact spans across various life domains, including social, professional and private dimensions (Table 5.7).

Table 5-7 Median scores (interquartile range) of impact of cluster headache on daily living

Domain	Total (n = 406)	ECH (n = 239)	CCH (n = 167)	p values[1]
General	9 (7 – 10)	8 (7 – 10)	10 (8 – 10)	< 0.001
Social	8 (6 – 10)	7 (5 – 8)	9 (8 – 10)	< 0.001
Professional	8 (7 – 10)	8 (6 – 9)	10 (8 – 10)	< 0.001
Private	8 (6 – 10)	8 (5 – 9)	9 (7 – 10)	< 0.001

ECH = episodic cluster headache, CCH = chronic cluster headache
[1]Based on Independent Samples Mann-Whitney U test
Median scores based on a 1 – 10 visual analog scale

A comparison of age of onset of CH and duration of illness with the CH-specific HRQoL questionnaire revealed that there were significantly higher mean total HRQoL scores in patients with earlier onset of headaches compared to those who developed CH later in life, as shown in Table 5.8, with Gabriel post hoc comparison test showing that the difference was highly significant between those who developed CH at a younger age and those who developed them at ≥ 41 years. There were no meaningful differences found based on the duration of illness.

Table 5-8 Comparison of CH-specific HRQoL scores and age of onset and duration of illness

Characteristic	Total HRQoL score		*p* values[1]
	Mean	SD	
Age of onset, years			< 0.001
≤ 20	73.0	18.8	
21 - 30	67.9	20.7	
31 - 40	64.4	21.9	
≥ 41	57.0	21.6	
Duration of illness, years			0.345
≤ 10	67.6	20.6	
11 - 20	65.8	21.5	
21 - 30	65.6	20.9	
≥ 31	61.2	23.5	

CH = cluster headache, HRQoL = health related quality of life, SD = standard deviation

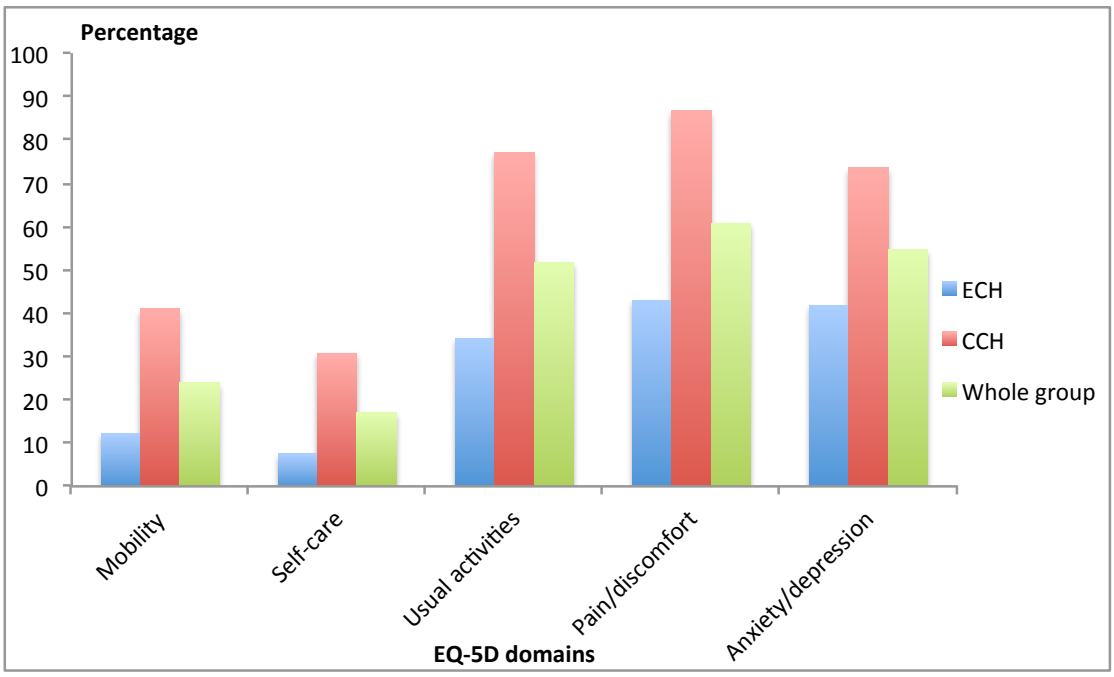
[1]Based on oneway ANOVA tests

5.3.c Generic HRQoL instruments

The generic HRQoL instruments used were the EQ-5D and SF-36 Health Survey.

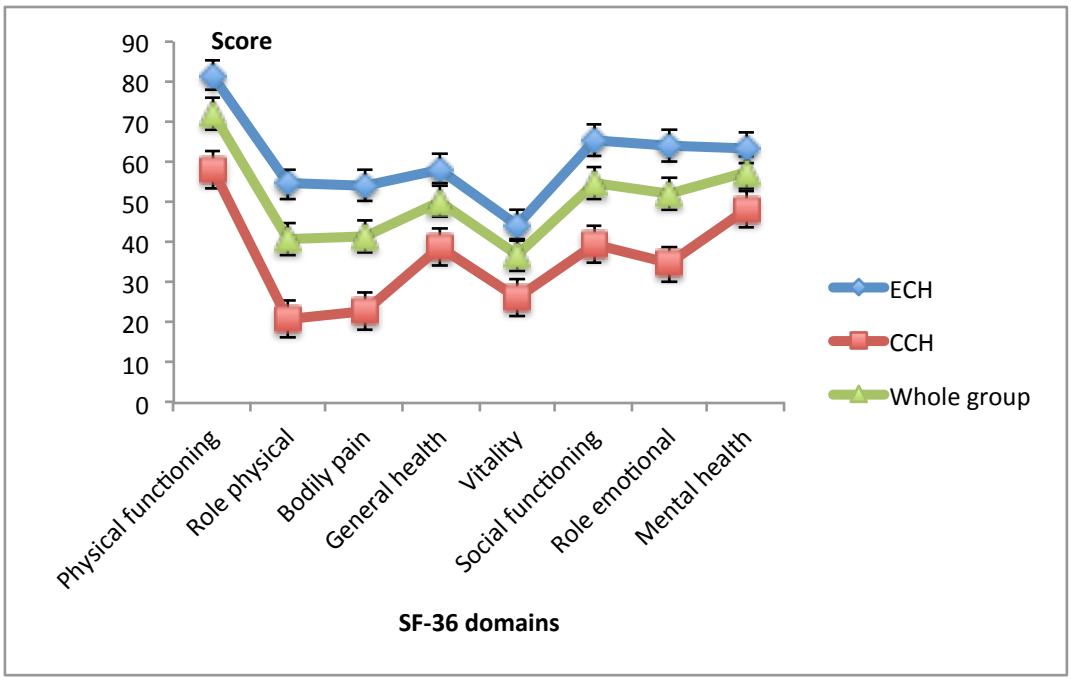
There were significant differences ($p < 0.001$) in EQ-5D scores between ECH and CCH patients in all domains, as shown in Figure 5.1. Forty-one percent of CCH patients reported problems in walking about compared to only 11.7% of ECH patients. Moreover, 30.5% of CCH patients had problems with self-care, such as washing or dressing themselves, compared to a mere 7.5% of ECH patients. Furthermore, more than 70% of CCH patients had problems with performing their usual activities, had some pain or discomfort and felt anxious or depressed. There was also a significant difference in the VAS score between ECH and CCH patients ($p < 0.001$), with the former have a median score of 72.0 and the latter 40.0 on a 0 to 100 scale, reflecting poorer health state in CCH.

Figure 5-1 Percentage of patients having problems in EQ-5D domains
EQ-5D = The European Quality of Life scale, ECH = episodic cluster headache, CCH = chronic cluster headache



Chronic CH patients had significantly reduced HRQoL compared to their episodic counterparts, as evident from the significantly lower scores in all domains of the SF-36 Health Survey ($p < 0.001$). As a whole group, the domains most affected were vitality, role physical and bodily pain, whilst the least affected was physical functioning (Figure 5.2).

Figure 5-2 Mean SF-36 scores of ECH and CCH patients, and the whole study sample
Error bars represent standard error of the mean
SF-36 = Short Form 36-item Health Survey, ECH = episodic cluster headache, CCH = chronic cluster headache



5.3.d Headache-specific HRQoL instrument

The MSQ v2.1 is scored from 0 to 100, with higher scores indicating better HRQoL. Patients with CH scored poorly on the MSQ v2.1, with the total median score for the whole group being 47.1 (range 0 – 80). The domain that had the lowest score was the role restrictive domain. Chronic CH patients scored significantly lower ($p < 0.001$) in all the three domains compared to ECH patients, as shown in Table 5.9.

Table 5-9 Median scores (interquartile range) of MSQ v2.1 scale for the study sample

MSQ domain	Total	ECH	CCH	*p* values[1]
Role restrictive	42.9 (20.0 – 65.7)	54.3 (29.3 – 80.0)	28.6 (11.4 – 51.4)	< 0.001
Role preventive	60.0 (35.0 – 75.0)	65.0 (45.0 – 80.0)	45.0 (21.3 – 65.0)	< 0.001
Emotional functioning	46.7 (20.0 – 73.3)	60.0 (31.7 – 80.0)	26.7 (6.7 – 53.3)	< 0.001
Total score	47.1 (24.3 – 68.6)	57.1(36.4 – 80.0)	31.4 (18.9 – 53.9)	< 0.001

MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire Version 2.1, ECH = episodic CH, CCH = chronic CH
[1]Based on Independent Samples Mann-Whitney U test

5.3.e Headache-specific disability instruments

The results of the statistical analysis of the headache-specific disability instruments used in the study are presented in Table 5.10.

The median MIDAS score for the whole study sample was 30.0 (range 0 - 270), with CCH patients having significantly higher scores than ECH patients (84.0 vs 13.0, $p < 0.001$). Based on the MIDAS disability grades, over half of the patients reported being severely disabled (56.8%), 8.1% were moderately disabled, 5.3% were mildly disabled and 29.8% reported minimal disability (Figure 5.3)

Patients with CCH had significantly higher mean HIT-6 score compared to ECH patients (65.0 vs 62.0, $p < 0.001$). The median HIT-6 score for the whole group was 63.0 (range 40 – 78), reflecting severe impact of headaches on patients' lives. The HIT-6 classification demonstrated that the majority of patients were severely impacted by their headaches (70.5%), 10.6% reported substantial impact, 11.9% had some impact whilst only 7.0% had little or no impact (Figure 5.4)

There were also statistically significant differences ($p < 0.001$) in the median HDI total scores between ECH (64.0) and CCH patients (76.0), as well as in the emotional and functional subscale scores. As a group in general, patients with CH had a median total

HDI score of 68.0 (range 4 – 100), indicating profound disability due to their headaches.

Table 5-10 Results of statistical analysis of the MIDAS, HIT-6 and HDI scales

Scale		Total	ECH	CCH	*p* values[1]
MIDAS		30.0 (3 – 104)	13.0 (0 – 53)	84.0 (27 – 173)	< 0.001
HIT-6		63.0 (58 – 68)	62.0 (55 – 67)	65.0 (61 – 70)	< 0.001
HDI					
	emotional	49.0 (44.0 – 52.0)	48.0 (44.0 – 52.0)	50.0 (45.0 – 52.0)	0.022
	functional	50.5 (48.0 – 56.0)	51.0 (48.0 – 56.0)	50.0 (48.0 – 55.0)	0.031
	total	68.0 (54.0 – 82.0)	64.0 (50.5 – 76.0)	76.0 (63.5 – 88.0)	< 0.001

MIDAS = The Migraine Disability Scale, HIT-6 = The Headache Impact Test 6 items, HDI = The Henry Ford Headache Disability Inventory, ECH = episodic cluster headache, CCH = chronic cluster headache
Scores shown are median scores (interquartile range)
[1]Based on Independent Sample Mann-Whitney U test

Figure 5-3 Headache-related disability assessed by the MIDAS scale
MIDAS = The Migraine Disability Scale, ECH = episodic cluster headache, CCH = chronic cluster headache

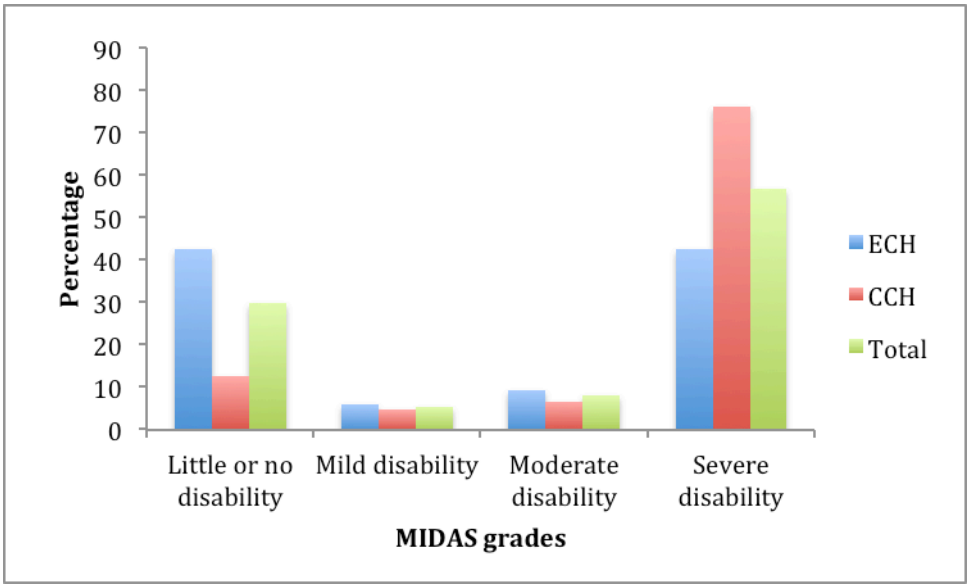
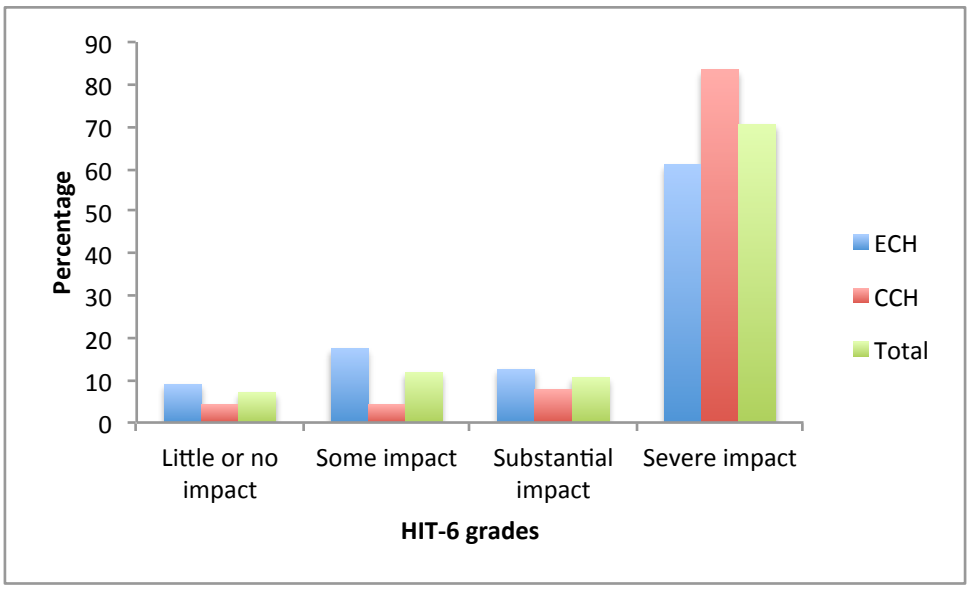


Figure 5-4 The impact of cluster headache according to HIT-6 grades
HIT-6 = The Headache Impact Test 6 items, ECH = episodic cluster headache, CCH = chronic cluster headache



According to the CH-specific HRQoL questionnaire, the mean total HRQoL scores for the study sample increased significantly with the MIDAS and HIT-6 classification groups (Table 5.11). Games-Howell post-hoc comparisons on the MIDAS scale revealed that the little or no and mild disability groups were significantly different from the severe disability group. Similarly, for the HIT-6 scale, the severely impacted group was significantly different from the others. Thus severe headache-related disability was associated with significantly diminished HRQoL.

Table 5-11 Comparison of CH-specific HRQoL score across MIDAS and HIT-6 classification groups

Scale	Total HRQoL score		*p* values[1]
	Mean	SD	
MIDAS			< 0.001
Little or no disability	55.5	24.7	
Mild disability	55.6	16.1	
Moderate disability	62.0	16.6	
Severe disability	72.9	17.4	
HIT-6			<0.001
Little or no impact	43.0	21.2	
Some impact	51.5	24.0	
Substantial impact	56.2	22.3	
Severe impact	71.5	17.6	

MIDAS = The Migraine Disability Scale, HIT-6 = The Headache Impact Test 6 items, CH = cluster headache, HRQoL = health related quality of life
[1]Based on Welch F tests

5.3.f Measures of psychological health

Anxiety and depression was measured by the HADS, which revealed that 64.1% of the patients had anxiety scores of ≥ 8, whilst 52.7% had depression scores of ≥ 8 (Table 5.12). The median anxiety score was 10.0 (range 0 – 21) and the median depression score was 8.0 (range 0 – 21). Chronic CH patients had significantly higher scores than ECH patients on both domains (anxiety 12.0 vs 8.0, $p < 0.001$, depression 11.0 vs 6.0, $p < 0.001$). More than three-quarters of CCH patients (78.4%) had anxiety scores of ≥ 8 compared to 53.9% of ECH patients, whilst 71.6% of the former had depression scores of ≥ 8 compared to 39.3% in the latter.

Table 5-12 Anxiety and depression scores of patients

	Total	ECH	CCH	*p* values[1]
HAD scale				
Anxiety score, median (interquartile range)	10.0 (6 – 14)	8.0 (4 – 12)	12.0 (8 -15)	< 0.001
Depression score, median (interquartile range)	8.0 (4 – 12)	6.0 (2 – 10)	11.0 (7 – 14)	< 0.001
Percentage of patients with scores ≥ 8				
Anxiety	64.1	53.9	78.4	< 0.001
Depression	52.7	39.3	71.6	< 0.001

ECH = episodic cluster headache, CCH = chronic cluster headache, HAD = Hospital Anxiety and Depression

[1]Based on Independent Samples Mann-Whitney U test and Chi-square test

The results of the Starkstein apathy scale are shown in Table 5.13. About 45% of patients had apathy scores of ≥ 14, indicating high apathy. There were significantly more CCH patients who had high apathy scores than ECH patients (56.5% vs 38.4%, $p = 0.001$), with the median apathy score in the former group being 16.0 (range 1 – 37) and the latter group having a mean apathy score of 11.0 (range 1 – 33).

Table 5-13 Results of the Starkstein apathy scale

	Total	ECH	CCH	*p* values[1]
Median score (interquartile range)	13.0 (8 – 18)	11.0 (7 – 16)	16.0 (10 – 22)	< 0.001
Percentage of patients having scores ≥ 14				0.001
Low apathy	54.4	61.6	43.5	
High apathy	45.6	38.4	56.5	

ECH = episodic cluster headache, CCH = chronic cluster headache
[1]Based on Independent Samples Mann-Whitney U test and Chi-square test

The median BHS score for the whole study sample was 5.0 (range 0 - 20), with CCH patients having significantly higher scores than ECH patients (9.5 vs 4.0, $p < 0.001$), as shown in Table 5.14. Based on the BHS classification grades, 21.1% of patients reported having feelings of severe hopelessness, 14.8% had moderate hopelessness, 27.5% had mild hopelessness and 36.6% reported minimal hopelessness.

Table 5-14 Results of the Beck Hopelessness Scale

	Total	ECH	CCH	*p* values[1]
Median score (interquartile range)	5.0 (2 – 13)	4.0 (2 – 8)	9.5 (4 – 17)	< 0.001
Percentage of patients within the classification grades				< 0.001
Minimal	36.6	47.6	21.3	
Mild	27.5	28.8	25.6	
Moderate	14.8	12.7	17.7	
Severe	21.1	10.9	35.4	

ECH = episodic cluster headache, CCH = chronic cluster headache
[1]Based on Independent Samples Mann-Whitney U test and Chi-square test

Patients with CCH had significantly higher median GHQ-28 scores compared to ECH patients (10.0 vs 5.0, $p < 0.001$), greatly exceeding the cut-off score ≥ 4 for this scale,

whilst the group as a whole had a median score of 7.0 (range 0 – 28), as shown in Table 5.15. Almost three-quarter of CCH patients (73.2%) scored ≥ 4, whereas 56.1% of ECH patients (p = 0.001), suggesting high proportion of patients having probable distress due to their headaches.

Table 5-15 Results of the GHQ-28 scale

	Total	ECH	CCH	p values[1]
Median score (interquartile range)	7.0 (1 – 14)	5.0 (1 – 12)	10.0 (3 -19)	< 0.001
Percentage of patients based on scores				0.001
Non-case	36.8	43.9	26.8	
Probable distress (scores ≥ 4)	63.2	56.1	73.2	

GHQ-28 = The General Health Questionnaire 28-items, ECH = episodic cluster headache, CCH = chronic cluster headache
[1]Based on Independent Samples Mann-Whitney U test and Chi-square test

Meanwhile, a comparison of the mean total HRQoL scores of the CH-specific HRQoL questionnaire between patients who reported associated anxiety or depression and those who did not, demonstrated that there were significant differences between the groups (Table 5.16). Patients with associated anxiety had significantly higher mean total HRQoL scores (78.9 ± 15.6 vs 54.6 ± 19.7, p < 0.001). Similarly, patients with associated depression also had poorer HRQoL (79.0 ± 16.1 vs 58.2 ± 20.7, p < 0.001) compared to those without.

A similar pattern was seen with apathy, with those reporting high apathy having significantly higher mean total HRQoL scores than the low apathy group (73.3 ± 19.4 vs 58.1 ± 20.2, p < 0.001). There was a linear increase in mean total HRQoL scores based on the classification groups of the BHS scale, with the severe hopelessness

group having significantly poorer HRQoL than those reporting minimal hopelessness. Patients who had probable psychological distress on the GHQ-28 scale also had significantly higher mean total HRQoL score than those without (71.5 ± 19.0 vs 54.3 ± 21.1, $p < 0.001$).

Table 5-16 Comparison of CH-specific HRQoL scores with measures of psychological health

Scale		Total HRQoL score		*p* values[1]
		Mean	SD	
HADS - Anxiety				< 0.001
	Non-case	54.6	19.7	
	Case	78.9	15.6	
HADS - Depression				< 0.001
	Non-case	58.2	20.7	
	Case	79.0	16.1	
Starkstein apathy				< 0.001
	Low apathy	58.1	20.2	
	High apathy	73.3	19.4	
BHS				< 0.001
	Minimal	53.7	21.2	
	Mild	64.0	19.0	
	Moderate	69.0	16.3	
	Severe	83.4	12.6	
GHQ-28				< 0.001
	Non-case	54.3	21.1	
	Probable distress	71.5	19.0	

CH = cluster headache, HRQoL = health related quality of life, SD = standard deviation, HADS= Hospital Anxiety and Depression scale, BHS = Beck Hopelessness Scale, GHQ-28 = The General Health Questionnaire 28-items
[1]Based on Independent Samples Mann-Whitney U test and Kruskall-Wallis oneway ANOVA test

5.3.g Other instruments used

The median total score or pain rating index (PRI) of patients measured by the MPQ was 45.0 (range 0 – 74). Chronic CH patients had significantly higher ratings of pain compared to episodic patients (48.0 vs 43.0, $p = 0.028$), although only sensory pain

showed meaningful differences between the two groups (Table 5.17). The PBC revealed that there were also significant differences in patients' reported behaviour to their pain, with CCH patients having higher median scores in all components, namely help-seeking behaviour, avoidance behaviour and complaint behaviour.

A higher proportion of CCH patients reported having low self-esteem on the RSES (44.8% vs 19.1%, $p < 0.001$) compared to their episodic counterparts. The median score of this scale was 18.0 (range 0 - 30) for the whole group, with significantly lower scores in the chronic group (15.0 vs 20.0, $p < 0.001$).

Episodic and CCH patients reported no significant differences in the number of people they could count on to provide support and their satisfaction with the support provided, as assessed by the social support scale. They have on average 2.0 people whom they can count on for practical support, with a satisfaction score of 6.0. Meanwhile, they could count on a similar number of people for emotional and mental support, with a satisfaction score of 6.0.

The Acceptance of Illness scale showed that 79.7% of patients had low scores, reflecting lack of acceptance and poor adjustment to their CH. This was more so for patients with chronic compared to ECH (89.4% vs 72.2%, $p < 0.001$). The median scores for the whole group and the ECH and CCH patients are shown in Table 5.17. The degree of stigma associated with CH is also significantly greater in CCH patients compared to episodics (mean ± SD, 11.3 ± 3.9 vs 8.6 ± 3.8, $p < 0.001$), as evaluated by the stigma scale.

Table 5-17 Results of statistical analysis of the MPQ, PBC, RSES, social support, Acceptance of Illness and stigma scale

Scale		Total	ECH	CCH	*p* values[1]
MPQ					
	Sensory	23.0 (15 - 29)	21.0 (14 – 28)	24.5 (17 – 31)	0.018
	Affective	9.0 (5 – 11)	9.0 (5 – 11)	9.0 (6 – 11)	0.086
	Evaluative	5.0 (4 - 5)	5.0 (4 – 5)	5.0 (4 – 5)	0.497
	Miscellaneous	10.0 (7 – 13)	9.0 (6 – 13)	10.0 (7 – 13)	0.449
	Total	45.0 (34 – 56)	43.0 (33 – 56)	48.0 (35 – 58)	0.028
PBC					
	Help-seeking	3.0 (1 – 4)	2.0 (1 – 4)	3.0 (2 – 4)	0.001
	Avoidance	16.0 (9 – 22)	13.0 (4 – 20)	19.0 (12 – 24)	< 0.001
	Complaint	7.0 (5 – 8)	7.0 (3 – 8)	7.0 (6 – 9)	0.007
RSES		18.0 (13.0 – 23.0)	20.0 (16.0 – 24.8)	15.0 (10.0 – 20.0)	< 0.001
Percentage of patients based on scores					< 0.001
	Low self-esteem	29.6	19.1	44.8	
	Normal range	54.9	58.9	49.1	
	High self-esteem	15.5	22.0	6.1	
Social support					
	Practical				
	Number of people	2.0 (0 – 8)	2.0 (0 -8)	2.0 (0 – 8)	0.913
	Satisfaction score (scale 1 - 6)	6.0 (1 – 6)	6.0 (2 – 6)	6.0 (1 – 6)	0.672
	Emotional and mental				
	Number of people	2.0 (0 – 9)	2.0 (0 – 9)	2.0 (0 -9)	0.943
	Satisfaction score (scale 1 - 6)	6.0 (1 – 6)	6.0 (1 – 6)	6.0 (1 -6)	0.583
Acceptance of Illness		21.0 (15 – 28)	24.0 (19 – 30)	17.0 (12 – 23)	< 0.001
Percentage of patients based on scores					< 0.001
	Low score	79.7	72.2	89.4	
	Medium score	11.6	17.2	4.3	
	High score	8.6	10.5	6.2	
Stigma scale, mean ± SD		9.7 ± 4.1	8.6 ± 3.8	11.3 ± 3.9	< 0.001

MPQ = McGill Pain Questionnaire, PBC = Pain Behaviour Checklist, RSES = The Rosenberg Self-Esteem Scale, ECH = episodic cluster headache, CCH = chronic cluster headache, SD = standard deviation

[1]Based on Independent Sample Mann-Whitney U test, two-samples t-test and Chi-square tests
Values are median scores (interquartile ranges), unless stated otherwise

A comparison of the RSES and Acceptance of Illness scale with the CH-specific HRQoL scales yielded the results shown in Table 5.18. Oneway ANOVA test with Hochberg's post-hoc comparison showed that patients with low self-esteem on the RSES had significantly poorer HRQoL compared to those with normal and high self-esteems. Similarly, those who had low scores on the Acceptance of Illness scale, reflecting poor acceptance and adaptation to their headaches, had significantly higher mean total HRQoL scores compared to those with medium and high scores.

Table 5-18 Comparison of CH-specific HRQoL scores with the RSES and Acceptance of Illness scale

Scale	Total HRQoL score		*p* values[1]
	Mean	SD	
RSES			< 0.001
Low self-esteem	80.9	13.6	
Normal range	62.4	19.8	
High self-esteem	48.4	19.7	
Acceptance of Illness			< 0.001
Low score	71.4	17.6	
Medium score	44.3	16.2	
High score	37.5	19.3	

CH = cluster headache, HRQoL = health related quality of life, RSES = The Rosenberg Self-Esteem Scale, ECH = episodic cluster headache, CCH = chronic cluster headache, SD = standard deviation
[1]Based on oneway ANOVA test and Kruskall-Wallis oneway ANOVA test

5.4 Discussion

This study was carried out to describe the sociodemographic and clinical characteristics of a large cohort of CH patients and specifically assess the impact or burden of their headache on their quality of life. HRQoL is a subjective assessment by patients of the impact of their headaches and its treatment on a range of life domains,

including physical, emotional, social and functional well-being. Thus, in order to cover all these aspects, a number of different instruments to measure these various dimensions of HRQoL were utilized. The instruments used included generic HRQoL scales, headache-specific HRQoL and disability scales, measures of psychological health and a range of other instruments measuring pain, pain behaviour, self-esteem, social support, acceptance of illness and stigma. To my knowledge, this is the largest study describing the characteristics and HRQoL of CH patients to date.

Sociodemographic and headache characteristics

The male to female ratio of the study sample was slightly lower than that reported elsewhere (2.1:1 vs 2.5 – 7.2: 1), possibly owing to increased awareness of the disorder in females, although a male preponderance still exists (1, 8). More than half were gainfully employed, although there were a significantly higher proportion of CCH patients who were unemployed, mainly due to disability. This is in accordance with the results from published studies, which have found that up to a third of CCH patients had lost their jobs due to their headache and are receiving invalidity allowance (161-163). Moreover, there were significantly less CCH patients in higher occupation class, which is in agreement with previous reports of career limitations in this group (161, 163).

Episodic CH patients in this study had a slightly higher mean age of onset (31.5 years) compared to a previous large prospective study (28.4 years) (8). However, in line with that study, patients with CCH also had significantly higher mean age of onset compared to episodics (35.0 years) (8). About 10% of patients in this study experienced side shifting of their headaches and 3.7% had bilateral attacks, despite CH being defined as a strictly unilateral headache. Furthermore, a similar proportion

(4.0%) had attacks lasting more than three hours, despite almost all patients having access to some form of abortive medication, the commonest being subcutaneous Sumatriptan and high dose and high flow rate oxygen. This is longer than the duration proposed by ICHD-3 beta for CH of 15 – 180 minutes (5). These differences may have arisen because about a third of patients (36.5%) were recruited from the headache clinic at The National Hospital for Neurology and Neurosurgery, which is a tertiary referral centre for headaches where a number of atypical and treatment-refractory cases are seen.

Half of the patients (50.0%) experienced pain in the maxillary and mandibular distributions of the trigeminal nerve. This is important from a dental point of view, as patients may initially seek dental treatment for the pain. Indeed, a study found that 45% of CH patients consulted a dentist prior to neurologic referral (282). Of these, 18% had unnecessary dental treatment instituted in an attempt to alleviate pain. Treatments received included tooth fillings and extractions, splint therapy, orthodontic treatment and maxillofacial surgery. Similarly, Bittar and Graff-Radford performed a retrospective study of 33 CH patients and reported that 42% of these patients were seen by dentists prior to referral to the pain management centre and underwent some form of dental treatment, without favourable outcome (283). An oral appliance was constructed for six (42%) of these patients, aimed to treat temporomandibular disorders (arthromyalgic group). Four patients had teeth extracted, three underwent coronoplasty (tooth grinding) procedures, and two had endodontic treatment. In this study, four patients reported consulting and obtaining a diagnosis of CH from a dentist, thus dental professionals should always remain vigilant during practice.

Interestingly, a greater proportion of patients with CCH reported having facial sweating, facial redness and ear discomfort associated with their attacks. The reason

for this is not known, however, it is speculated that there may be increased sympathetic overactivity in this patient group compared to the episodic group.

More than half of the CH patients reported having a warning symptom, similar to previous reports, which can be divided into premonitory and prodromal symptoms (164, 284, 285). The former are symptoms prior to a cluster bout, whereas the latter are those experienced just before an attack (284). Most of the patients who reported prodromal symptoms usually had them within 10 – 30 minutes before their attack. This can present in various forms, such as having a dull ache or pain usually local to the site of their attack, changes in vitality or mood, stiffness of the neck or shoulders or onset of cranial autonomic features or restlessness similar to that experienced during an attack. Meanwhile, ECH patients reported premonitory symptoms of a dull ache and tiredness up to four weeks before the onset of their bout. Blau and Engel (1998) have divided these symptoms into local vasomotor, muscular and neurological groups, and proposed that their existence may have pathogenetic implications (285).

Despite the differences discussed above, the demographic characteristics of CH patients in this study are comparable to those that have been reported previously (1, 8, 164)

Health related quality of life

The results from this study demonstrate that CH has a significant impact on patients' HRQoL, as evaluated from the various instruments used. The impact is greater for CCH patients compared to those with ECH, as shown by the significantly worse scores for the former in all generic and headache-specific HRQoL and disability scales. This is in contrast to that reported by D'Amico and colleagues who did not

find any significant differences in HRQoL between ECH and CCH patients, although their sample size was much smaller (56 CH patients) (162).

On the EQ-5D, patients reported having most problems in the pain/discomfort domain, which is in agreement with the excruciating pain intensity reported by > 70% of CH patients in this study. This also correlated with the pronounced limitation in bodily pain domain of the SF-36 Health Survey and the high total pain rating index on the MPQ.

Patients with CCH had significantly worse scores in all domains of the SF-36 Health Survey compared to ECH patients. The domain least affected was physical functioning, which measures the ability to perform a variety of physical activities. This is in accordance with the findings of previous studies that found that physical functioning was well preserved in CH patients, with no significant differences found compared to migraineurs, headache-free controls and normative data (3, 4, 162). On the other hand, vitality domain, which measures energy level and fatigue, was the most affected in this study sample. Taking into account the prevalence of nocturnal attacks in this disorder and the mean frequency of daily attacks (3.6) in the study sample, this impact on vitality was not surprising. However, CCH patients had lowest scores in role physical domain, which suggests that their headaches mostly interfere with their usual daily activities.

This correlated with their scores on the usual activities domain of the EQ-5D, whereby 77.1% of CCH patients reported having problems performing usual activities such as work, study, housework, family or leisure activities. Furthermore, patients scored poorly on the role restrictive domain of the MSQ v2.1, suggesting that their CH limits their ability to perform daily activities. Moreover, headache-disability scores were all significantly worse in this group, with 76.3% having severe disability

on the MIDAS and a profound 83.5% being severely impacted based on the HIT-6 scale. This is in contrast to the minute differences found in headache-related disability between ECH and CCH patients in a previous study (161). This high functional impairment experienced by CCH patients may account for the higher levels of unemployment seen in this group.

The high disability associated with this disorder has been well described, which also extends to family life (163, 164, 167). Jensen and colleagues found that about 61% of patients felt that their headache impacted on their family life and they have had to depend on help from family and friends (163). Data from this study show that patients are satisfied with the support available around them, having about two people whom they can really count on to provide practical and emotional or mental support. This is usually their significant other as approximately three-quarters of patients are married or cohabiting, though they also usually seek support from parents, siblings, children and friends.

Taking into account the excruciating pain and highly disabling nature of CH, it is therefore not surprising that patients have a hard time accepting and adjusting to the disorder. This is demonstrated from the high percentage of patients who scored poorly on the Acceptance of Illness scale. This suggests that there is a strong negative emotion associated with CH. Psychiatric comorbidity in primary headache disorders, specifically migraine, is well known, and has also been recently reported in CH (115, 161, 164, 286). This study found that half of patients reported symptoms of depression and about 60% met the HADS criteria for anxiety, with CCH patients fairing worse. Similar findings were seen from the anxiety/depression domain of the EQ-5D scale. Moreover, about 60% of patients had scores above the cut off point for the GHQ-28 scale, which is a screening tool for psychiatric disorders and only about a third of

patients did not report having feelings of hopelessness. Furthermore, patients also have low self-esteem and high apathy scores, with about 60% reporting feeling self-conscious and avoiding other people as a result of their headaches. These findings go in line with the agarophobia and suicidal tendencies often described in CH patients, whereby Jurgens and colleagues found that 33% of chronic and 15% of ECH patients had symptoms of the former, whilst 22% of chronic and 15% ECH patients had the latter (161).

Thus, CH has an impact on physical, mental, social and functional wellbeing, which are the elements of HRQoL. This overall impact is reflected in their self-reported scores on a visual analog scale, whereby when asked to score how CH has changed their life in general on a scale of 1 – 10, with 1 being a little and 10 a lot, the majority of patients (83%) scored ≥ 7 and 41% indicated it changed their life a lot (score of 10).

Effect of these factors on the CH-specific HRQoL scores

Age of onset of CH had a significant effect on HRQoL, with earlier onset associated with poorer outcome. The same pattern was found based on patients' current age, with younger patients (<45 years) having significantly diminished HRQoL. This may be due to the related work, family and social commitments that one tends to have around this time period, which is often the most productive working, family and social years of their life. This explains the significant effect employment status has on HRQoL, whereby those who are unemployed feel the most burden since they may no longer be able to provide for themselves and their family. Similarly, career limitations due to CH have a profound impact on HRQoL. Patients who are single or divorced/separated also had poorer HRQoL compared to those who are married/cohabiting or widowed,

possibly due to the absence or loss of a reliable support system that they can depend on.

There was no significant difference in HRQoL based on the duration of the disorder. This is in concordance with the finding from this study that CH patients have poor acceptance of their headache, thus the impact on their HRQoL remains consistent throughout the years that they suffer with the disorder. Furthermore, the poorer their acceptance of their CH, then the worse their HRQoL tends to be.

An inverse relationship between disability and HRQoL has been previously reported in migraines, though its effect on CH has not been studied (108, 126). The data from this study supports this relationship, with patients who were severely disabled or impacted by their headaches having significantly diminished HRQoL.

With regards to emotional and mental wellbeing, patients who had any psychiatric complaints, such as symptoms of anxiety, depression, apathy, hopelessness or had low self-esteem had significantly poorer HRQoL compared to their non-symptomatic counterparts. This is further supported by the significantly diminished HRQoL scores in patients who met the criteria for probable psychiatric distress on the GHQ-28 scale. This demonstrates that emotional and mental wellbeing are important constructs of HRQoL.

Conclusion

This study has therefore provided detailed information of the sociodemographic and clinical characteristics of a large cohort of CH patients. Furthermore, it provides supporting evidence of the significant impact CH has on patients' HRQoL and the high prevalence of psychiatric complaints patients have. This impact is significantly greater in patients who have CCH than those who suffer the episodic variant, which is

not surprising as their headaches are unremitting. The effects that certain variables have on reported HRQoL have also been described. These are likely to play a role in predicting or determining HRQoL in this population, although further work is required to assess the weight or magnitude of effect they have on HRQoL. In particular, the consistent diminished HRQoL scores in patients exhibiting symptoms of emotional or mental distress highlights the importance of proper headache management, which requires not only management of the headache pain itself, but also of any associated comorbidity.

Chapter 6 General discussion

6.1 Overview

Cluster headache is known to be an excruciatingly painful headache disorder, which although is often remitting, can still have a huge impact on patients' lives. Even though the disorder can be managed quite effectively, it remains largely empirically based. Thus there is great emphasis on and a high degree of interest in trying to unravel the pathophysiological basis of the disorder and in assessment of the burden it imposes on patients' lives. The aim of this thesis was to improve understanding of the underlying mechanisms in CH through a range of different studies. This chapter summarizes the findings from the various studies within this thesis and discusses the limitations and future directions in this field.

6.1.a Summary of findings

i Neuroimaging study

The GONB is a widely used transitional treatment in CH, with proven efficacy and safety (53, 56, 62, 63, 65). An fMRI study utilizing ASL was conducted in CH patients receiving their first GONB to map and identify changes in rCBF relating to brain responses prior to and following the treatment. As evident from previous functional neuroimaging studies in CH, the hypothalamus is likely to have a pivotal role in CH pathophysiology (18, 19, 29, 37, 40, 41). From this fMRI study, the posterior hypothalamic area was also found to demonstrate significant increases in rCBF during the interictal period, thus further supporting the previous findings. Moreover, there were significant increases in rCBF in a number of brain regions previously activated in other pain studies. In particular, increases were observed in the

left orbitofrontal cortex, left basal ganglia, left amygdala, left hippocampus and parahippocampal gyrus, left lateral posterior thalamic and pulvinar nuclei and bilaterally in the brainstem prior to the GONB. Since each of these regions are known to have a role in various aspects of pain processing, specifically the sensory-discriminative, affective/emotional and cognitive processing of pain, as well as in the salience detection system, it is likely that these regions represent an interconnected network of structures that integrates the pain experience of CH, reflecting a central permissive state that can lead to attacks. Similar to the previous study on paroxysmal hemicrania, it is hypothesized that this system remains activated at a subthreshold level in the interictal CH period, and attacks triggered once a threshold level for pain is reached (246). Following the GONB, there were reductions in rCBF in these regions, suggesting a possible winding down of this network.

ii Saccadometry study

The saccadometry study showed that the reaction time distributions of CH patients differed significantly from age- and sex-matched controls in all measurement parameters. In particular, the mean saccadic latencies of CH patients were longer with greater variability compared to controls. However, significantly less CH patients exhibited an early saccade, with smaller variability in the distribution of the early saccades compared to controls. These findings suggest that there is delay in the decision-making process of saccadic information in this population. Whilst this delay can occur within any of the neural pathways involved in saccadic generation, the reduced proportion of early saccades in CH patients suggests that the basal ganglia may have a role in contributing to this impairment. This is because the basal ganglia is tonically inhibitory and exerts descending inhibitory input to the SC, which constitutes the “final common pathway” for generation of saccades (74, 250). Thus

the longer mean saccadic latencies and reduced proportion of early saccades in CH may reflect the presence of a tight inhibitory control over the SC, which stems from the basal ganglia.

As far as the increased variability is concerned, a previous study in migraineurs found reduced variability in reaction time distributions compared to controls, which they attributed to a functional deficit in the noradrenergic system (75). Whilst this is also likely to explain the findings of this study, it is also possible that variability may arise from the extent of underlying pathology in CH, which may affect different elements controlling saccadic generation, as was proposed by Barker and Michell (73).

iii Quality of life study

Due to the high disability and impact often reported by CH patients and the lack of a specific HRQoL measure in this patient group, a self-administered "Cluster headache specific quality of life" (CHQ) scale was developed and validated. A three-step approach was employed in the scale development: item generation; item reduction and scale development; and, scale validation and reliability testing. A literature review, semi-structured patient interviews and expert panel consultation yielded a 54-item questionnaire, which was pre-tested in a sample of CH patients and subsequently reduced to 47 items. In stage 2, the revised scale was administered to CH patients attending a tertiary headache clinic and those registered with a patient group. A total of 406 completed questionnaires were received. To assess test-retest reliability, a subsample (N=56) completed the scale on a second occasion, two weeks after the first. Item reduction and exploratory factor analysis led to 28-items, grouped into four subscales labeled "restriction of activities of daily living", "impact on mood and interpersonal relationships", "pain and anxiety", and "lack of vitality". The final CH-specific HRQoL scale, the CHQ, demonstrated satisfactory internal consistency

(Cronbach's alpha > 0.5) and test-retest reliability (correlation coefficient > 0.7), with good internal construct validity (range 0.52 – 0.75) and convergent validity with other HRQoL measures.

Using the same patient dataset, the sociodemographic and headache characteristics of CH patients was also described. Of particular interest was an assessment of their HRQoL, specifically to evaluate for differences between ECH and CCH patients. The sociodemographic and headache characteristics of CH patients in this study are comparable to those reported in previous studies (8, 164). This study found that younger patients and those who had an earlier age of onset of their CH had significantly diminished HRQoL, possibly owing to the greater impact it has on the productive years of life. Patients who were single or divorced/separated also had poorer HRQoL compared to those who were married/cohabiting or widowed.

In terms of HRQoL, the findings from this study support previous studies that reported that CH is associated with high disability and has significant impact on patients' lives (3, 162, 166). There was an inverse relationship between disability and HRQoL, with those who were severely disabled or impacted by their headaches having significantly diminished HRQoL. Moreover, patients with CCH were shown to have significantly poorer HRQoL compared to ECH patients, as evident from their significantly worse scores in all generic and headache-specific HRQoL and disability scales. This high functional impairment may account for the higher levels of unemployment reported by CCH patients, which then impacts further on their HRQoL as they are unable to provide for themselves and their family, thus creating a vicious cycle. Furthermore, CH patients were found to have a hard time accepting and adjusting to their headaches, therefore it was not surprising that at least half of them reported symptoms of depression and anxiety, with CCH patients faring worse. This

theme of an associated psychiatric comorbidity was consistent across all the measures used in this study, with substantial reports of having feelings of hopelessness, low self-esteem and high apathy associated with the headaches, which had a significant impact on HRQoL.

iv Overall conclusions based on findings

The attempt of this thesis was to gain further insight into the underlying processes involved in CH by taking a mixed methods approach in the assessment of the disorder, using fMRI and saccadometry studies, whilst also studying the disability and resultant impact it has on patients' quality of life. The increase in rCBF in the posterior hypothalamus observed in the fMRI study, which was performed during the interictal state, further supports the view that this structure may have a crucial role in CH pathophysiology. Previous neuroimaging studies have reported ipsilateral hypothalamic activation in CH, which is in keeping with the unilaterality.of attacks that are characteristic of this disorder (18, 19, 29, 37). Considering that the majority of patients in this study had left-sided attacks, these lateralized increases in rCBF on the left side may reflect this laterality, although further work with a larger dataset is required to confirm or refute this finding.

Of interest to note were the increases in rCBF in other brain structures during this state. In particular, increases were observed in the orbitofrontal cortex, basal ganglia, amygdala, hippocampus, parahippocampal gyrus and posterior thalamus, which were all strictly unilateral, whilst that in the brainstem was bilateral. The increases in rCBF in these structures, which are known to have various roles in the processing of pain, were somewhat unexpected given that patients were headache-free during scanning. Therefore this implies that during a bout, there are neuroplastic changes within the central nervous system of CH patients leading to a persistent activation of this system,

and hence reflecting a central permissive state that can lead to attacks, with subsequent reductions in rCBF occurring following treatment, in this case, a GONB.

The discrete clusters of increased rCBF in the left basal ganglia extending to the left posterior hypothalamus and in the brainstem involving the red nucleus and substantia nigra somewhat answers the debate about the exact location of activation seen in the landmark PET study by May and colleagues (18, 287). This study provides evidence that both the posterior hypothalamus and the midbrain tegmentum show changes during the interictal state. Given that these structures are known to be involved in the processing and modulation of pain, they are therefore likely to form part of a network that is crucial in CH pathophysiology. Moreover, similar observations have also been reported in PET studies of PH and HC, whose clinical features overlaps with the TACs, thus suggesting a shared pathophysiology (44, 246).

Another interesting finding from this thesis was the correlation between the neuroimaging and saccadometry data. In particular, the basal ganglia or its constituent nuclei is a region that has been repeatedly reported to be activated in neuroimaging studies of CH, although not much emphasis has been placed on these observations, possibly due to the assumption that this region has a role in pain processing in general (17, 19, 37). However, findings from the fMRI study showing increases in rCBF during the interictal period when patients are headache-free begs the question of whether it has a more important role to play in CH. Furthermore, metabolic changes within the basal ganglia have also been reported in a PET study of CH patients scanned in and out of a bout compared to healthy controls, which the authors speculate may be associated with a dysfunction of the pain-modulating circuits in CH patients (288).

Brainstem activations have also been previously reported in CH and the other TACs, thus implying their probable crucial role in the underlying pathophysiology (44, 156, 217, 220). Indeed, the saccadometry study findings of increased mean saccadic latencies in CH patients, with reduced number of early saccades, suggest that the basal ganglia is exerting greater inhibitory control over the SC, and therefore is holding up the generation of visual saccades. Meanwhile the higher variability in saccadic reaction time is suggestive of a dysfunction within the noradrenergic system.

As previously discussed, there have been several reports of impaired dopaminergic and noradrenergic systems in CH. Dopamine agonist and antagonists have been shown to initiate and control CH attacks respectively (227-230). Increased levels of platelet dopamine have been observed in ECH patients, both during and outside of a bout, with blunted 24-hour prolactin production in CH patients and reduced response to thyrotropin-releasing hormone (231, 232). A recent study also found impaired increase in growth hormone levels following an apomorphine challenge in CH patients outside a bout, suggesting decreased sensitivity of dopaminergic neurons (233). Therefore, taking into account that the substantia nigra, one of the nuclei within the basal ganglia, is the main source of dopamine within the brain, it is therefore tempting to speculate that the basal ganglia or possibly the dopaminergic system has an important contribution to the neural mechanisms underlying CH. Meanwhile, reports of efficacy of Clonidine and Tizanidine as preventative treatments, and altered platelet levels of adrenaline and noradrenaline in all stages of CH also suggest the possibility of dysfunction within the noradrenergic system (253, 255, 256). Hence, it is proposed that there may be impairment involving both the noradrenergic and dopaminergic systems in CH.

In light of these findings, a reinterpretation of the structures thought to be involved in CH pathophysiology may be necessary. Whilst the hypothalamus, which has long been viewed as the central generator of the disorder, may have a pivotal role, it is highly likely that other structures, such as the basal ganglia and/or brainstem, may act in synchrony with it and therefore have crucial roles in CH pathophysiology.

With regards to quality of life, this thesis provides evidence to support that CH is a highly disabling disorder, with significant impact on everyday life. This impact is greater for patients who have the chronic variant, which was expected, due to the recurring nature of their headaches with no significant remission periods. There were also high levels of psychiatric comorbidity associated with this disorder, with diminished scores on all measures of emotional and mental well-being. Furthermore, these symptoms feed into and influence their HRQoL scores. Therefore, this reinforces the need for proper headache management, which takes into account these comorbidities along with providing pain relief.

It was therefore befitting that the first patient reported outcome measure to assess quality of life specifically for CH was developed and validated. A three-step approach was employed in the development of this scale, which following standard item reduction procedures, led to the final 28-item CHQ scale. The scale consisted of four domains, namely "restriction of activities of daily living", "impact on mood and interpersonal relationships", "pain and anxiety", and "lack of vitality", and has been demonstrated to have satisfactory internal consistency (Cronbach's alpha > 0.5) and test-retest reliability (correlation coefficient > 0.7), with good internal construct validity (range 0.52 – 0.75) and convergent validity with other widely used HRQoL measures.

6.2 Clinical implications and future research

6.2.a Neuroimaging study

The fMRI study will be continued to allow for further recruitment of patients to enable a fair comparison between responders and non-responders to the GONB. In doing so, this will also circumvent the issue of the order confound. Additionally, this study is also intended to be expanded by adding another scanning session (outside of a bout), either before or after they have had the GONB, which would further account for the potential confounding order effect.

Since the increase in rCBF seen in this study was confined to the left posterior hypothalamus, despite some patients having right-sided attacks, larger patient numbers would also be able to peter out analysis depending on laterality of attacks. On the other hand, future studies could also render recruitment of patients to be as homogeneous as possible, for example including those having strictly left-sided attacks only, to test for presence of true ipsilateral activation. Another interesting question that arises from this study is the role of the increases in rCBF seen in the brainstem of CH patients. A resting-state BOLD fMRI study can be undertaken in the future to test the hypothesis of functional connectivity between the spinal trigeminal nucleus and the hypothalamus.

6.2.b Saccadometry study

As previously mentioned in Chapter 3, a sensitivity and specificity analysis performed on the saccadometric data showed that up to 81% of individuals could be correctly assigned a diagnosis of CH by saccadometry alone, therefore suggesting its potential to be used as a diagnostic tool. However, this was in comparison to a group of healthy controls. Since CH in the main has highly stereotypical characteristics, diagnosis of

the disorder is largely based on a detailed clinical history. Thus the use of saccadometry on its own in diagnosis of CH is limited at this stage. Further work on a larger dataset, with inclusion and comparison to other headache disorders may allow a better determination of its sensitivity and specificity, and it may then have a better place as a tool to aid diagnosis of complex cases. A comparison of saccadic reaction time distributions of CH patients with those having other headache disorders may also allow identification of the underlying neural mechanisms of the different headache disorders.

Following on from the correlations seen between the neuroimaging findings and the saccadometry data, it is of interest to determine for changes, if any, in saccadic reaction time in CH patients inside and outside of a bout, as well as following treatment, such as the GONB. Hence, there is intention to extend the saccadometry study to run in parallel with the neuroimaging study, thus hopefully allowing an improved understanding of the functional impairment and neural mechanisms involved in CH. Depending on the results from this future study, there may also be potential in using saccadometry as an objective measure to monitor change following preventive or surgical treatment, as has been done in Parkinson's disease (72).

6.2.c Quality of life study

With regards to future work, the next stage in the validation of the CHQ will be an assessment of its sensitivity to capture change in HRQoL over time and following medical and surgical treatments of CH. Further studies will also need to be performed in other community populations as the development and validation of this scale was based solely on a sample of CH population in the United Kingdom. Additionally, further work on identification of factors that predict quality of life in CH would be

valuable in steering clinical management to focus on aspects of the disease that would help enhance quality of life of the patients with CH.

6.3 Final conclusion

CH is a highly disabling primary headache disorder and one of the main challenges faced by clinicians and patients is the poor understanding of its underlying mechanisms. Until such a time when the pathophysiological basis of the disorder is unraveled and treatment can be focused on the cause, current management centers on pain relief and improvement of quality of life of those affected. The various studies performed within this thesis have allowed us a better insight into the possible mechanisms associated with this disorder, as well as the significant impact it has on patients' lives. However, whilst this thesis has managed to identify several structures and hypothesized on the possible systems that may be dysfunctional, further work needs to be undertaken to clarify their potential role in CH pathophysiology. To allow better assessment of this impact, the CHQ scale has been developed, which is intended to be used in clinical practice and in clinical trials as an objective patient-reported outcome measure.

REFERENCES

1. Matharu M, Goadsby P. Trigeminal Autonomic Cephalalgias: Diagnosis and Management. In: Silberstein S, Lipton R, Dodick D, editors. *Wolff's Headache and Other Head Pain*. 8th ed. New York: Oxford University Press; 2007. p. 379-40.
2. May A. Cluster headache: pathogenesis, diagnosis, and management. Lancet. 2005;366(9488):843-55.
3. Solomon GD, Skobieranda FG, Gragg LA. Does quality of life differ among headache diagnoses? Analysis using the medical outcomes study instrument. Headache. 1994;34(3):143-7.
4. Ertsey C, Manhalter N, Bozsik G, Afra J, Jelencsik I. Health-related and condition-specific quality of life in episodic cluster headache. Cephalalgia. 2004;24(3):188-96.
5. (IHS) HCCotIHS. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.
6. Balasubramaniam R, Klasser GD. Trigeminal autonomic cephalalgias. Part 1: cluster headache. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics. 2007;104(3):345-58.
7. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160.
8. Bahra A, May A, Goadsby PJ. Cluster headache: A prospective clinical study with diagnostic implications. Neurology. 2002;58(3):354-61.
9. Russell MB. Epidemiology and genetics of cluster headache. Lancet Neurology. 2004;3(5):279-83.
10. Balasubramaniam R, Klasser GD, Delcanho R. Trigeminal autonomic cephalalgias: a review and implications for dentistry. Journal of the American Dental Association. 2008;139(12):1616-24.
11. Leone M, Russell MB, Rigamonti A, Attanasio A, Grazzi L, D'Amico D, et al. Increased familial risk of cluster headache. Neurology. 2001;56(9):1233-6.
12. El Amrani M, Ducros A, Boulan P, Aidi S, Crassard I, Visy JM, et al. Familial cluster headache: A series of 186 index patients. Headache. 2002;42(10):974-7.
13. Kudrow L, Kudrow DB. Inheritance of cluster headache and its possible link to migraine. Headache. 1994;34(7):400-7.
14. Goadsby PJ, Cittadini E, Burns B, Cohen AS. Trigeminal autonomic cephalalgias: diagnostic and therapeutic developments. Current Opinion in Neurology. 2008;21(3):323-30.
15. Rozen TD. Trigeminal Autonomic Cephalalgias. Continuum. 2006;12(6):170-93.
16. Nelson RF, du Boulay GH, Marshall J, Russell RW, Symon L, Zilkha E. Cerebral blood flow studies in patients with cluster headache. Headache. 1980;20(4):184-9.
17. Hsieh JC, Hannerz J, Ingvar M. Right-lateralised central processing for pain of nitroglycerin-induced cluster headache. Pain. 1996;67(1):59-68.
18. May A, Bahra A, Büchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet. 1998;352(9124):275-8.
19. May A, Bahra A, Buchel C, Frackowiak RSJ, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology. 2000;55(9):1328-35.

20. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. The Lancet Neurology. 2002;1:251-7.
21. Matharu M, Silver N. Cluster headache. Clin Evid (Online). 2008.
22. Chong SM. Headache syndromes presenting with facial pain and autonomic features. In: Zakrzewska JM, Harrison SD, editors. Assessment and Management of Orofacial Pain: Elsevier; 2002. p. 209-45.
23. May A. The role of imaging in the pathophysiology and diagnosis of headache. Current Opinion in Neurology. 2005;18(3):293-7.
24. Schoenen J. Cluster headaches-central or peripheral in origin? The Lancet. 1998;352(9124):253-5.
25. Leone M, Frediani F, D'Amico D, Patruno G, Valentini S, Parati EA, et al. Dexamethasone suppression test, melatonin and TRH-test in cluster headache. Ital J Neurol Sci. 1992;13(3):227-32.
26. Kudrow L. Plasma testosterone levels in cluster headache preliminary results. Headache. 1976;16(1):28-31.
27. Waldenlind E, Gustafsson SA, Ekbom K, Wetterberg L. Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. J Neurol Neurosurg Psychiatry. 1987;50(2):207-13.
28. Holle D, Obermann M. Cluster headache and the hypothalamus: causal relationship or epiphenomenon? Expert Rev Neurother. 2011;11(9):1255-63.
29. Sprenger T, Boecker H, Tolle TR, Bussone G, May A, Leone M. Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology. 2004;62(3):516-7.
30. Norris JW, Hachinski VC, Cooper PW. Cerebral blood flow changes in cluster headache. Acta Neurologica Scandinavica. 1976;54(4):371-4.
31. Krabbe AA, Henriksen L, Olesen J. Tomographic determination of cerebral blood flow during attacks of cluster headache. Cephalalgia. 1984;4(1):17-23.
32. Gawel MJ, Krajewski A, Luo YM, Ichise M. The cluster diathesis. Headache. 1990;30(10):652-5.
33. Sjaastad O, Rinck P. Cluster Headache: MRI Studies of the Cavernous Sinus and the Base of the Brain. Headache: The Journal of Head and Face Pain. 1990;30(6):350-1.
34. Sianard-Gainko J, Milet J, Ghuysen V, Schoenen J. Increased parasellar activity on gallium SPECT is not specific for active cluster headache. Cephalalgia. 1994;14(2):132-3.
35. Schuh-Hofer S, Richter M, Israel H, Geworski L, Villringer A, Munz DL, et al. The use of radiolabelled human serum albumin and SPECT/MRI co-registration to study inflammation in the cavernous sinus of cluster headache patients. Cephalalgia. 2006;26(9):1115-22.
36. May A, Kaube H, Buchel C, Eichten C, Rijntjes M, Juptner M, et al. Experimental cranial pain elicited by capsaicin: a PET study. Pain. 1998;74(1):61-6.
37. Morelli N, Pesaresi I, Cafforio G, Maluccio MR, Gori S, Di Salle F, et al. Functional magnetic resonance imaging in episodic cluster headache. Journal of Headache and Pain. 2009;10(1):11-4.
38. May A, Ashburner J, Buchel C, McGonigle DJ, Friston KJ, Frackowiak RS, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nature Medicine. 1999;5(7):836-8.
39. Matharu M. Functional and structural neuroimaging in primary headache disorders: University College London; 2006.

40. Lodi R, Pierangeli G, Tonon C, Cevoli S, Testa C, Bivona G, et al. Study of hypothalamic metabolism in cluster headache by proton MR spectroscopy. Neurology. 2006;66(8):1264-6.
41. Wang SJ, Lirng JF, Fuh JL, Chen JJ. Reduction in hypothalamic H-1-MRS metabolite ratios in patients with cluster headache. Journal of Neurology Neurosurgery and Psychiatry. 2006;77(5):622-5.
42. Holle D, Katsarava Z, Obermann M. The hypothalamus: specific or nonspecific role in the pathophysiology of trigeminal autonomic cephalalgias? Curr Pain Headache Rep. 2011;15(2):101-7.
43. Holle D, Naegel S, Krebs S, Gaul C, Gizewski E, Diener HC, et al. Hypothalamic gray matter volume loss in hypnic headache. Ann Neurol. 2011;69(3):533-9.
44. Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RS, Goadsby PJ. Posterior hypothalamic and brainstem activation in hemicrania continua. Headache. 2004;44(8):747-61.
45. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007;47(10):1418-26.
46. Tepper SJ, Stillman MJ. Cluster headache: potential options for medically refractory patients (when all else fails). Headache. 2013;53(7):1183-90.
47. May A, Leone M, Boecker H, Sprenger T, Juergens T, Bussone G, et al. Hypothalamic deep brain stimulation in positron emission tomography. Journal of Neuroscience. 2006;26(13):3589-93.
48. Tyagi A, Matharu M. Evidence base for the medical treatments used in cluster headache. Curr Pain Headache Rep. 2009;13(2):168-78.
49. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. Neurology. 2010;75(5):463-73.
50. Ashkenazi A, Schwedt T. Cluster headache--acute and prophylactic therapy. Headache. 2011;51(2):272-86.
51. May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. European Journal of Neurology. 2006;13(10):1066-77.
52. Evers S. Pharmacotherapy of cluster headache. Expert Opin Pharmacother. 2010;11(13):2121-7.
53. Peres MFP, Stiles MA, Siow HC, Rozen TD, Young WB, Silberstein SD. Greater occipital nerve blockade for cluster headache. Cephalalgia. 2002;22(7):520-2.
54. Levin M. Nerve blocks and nerve stimulation in headache disorders. Techniques in Regional Anesthesia & Pain Management. 2009;13(1):42-9.
55. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Occipital nerve blockade in chronic cluster headache patients and functional connectivity between trigeminal and occipital nerves. Cephalalgia. 2007;27(11):1206-14.
56. Afridi SK, Shields KG, Bhola R, Goadsby PJ. Greater occipital nerve injection in primary headache syndromes--prolonged effects from a single injection. Pain. 2006;122(1-2):126-9.
57. Young WB. Blocking the greater occipital nerve: Utility in headache management. Current Pain and Headache Reports. 2010;14(5):404-8.
58. Levin M. Nerve blocks and nerve stimulation in headache disorders. Techniques in Regional Anesthesia & Pain Management. 2009;13:42-9.
59. Poletti CE. C2 and C3 Pain Dermatomes in Man. Cephalalgia. 1991;11(3):155-9.

60. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Functional connectivity between trigeminal and occipital nerves revealed by occipital nerve blockade and nociceptive blink reflexes. Cephalalgia. 2006;26(1):50-5.
61. Piovesan EJ, Kowacs PA, Tatsui CE, Lange MC, Ribas LC, Werneck LC. Referred pain after painful stimulation of the greater occipital nerve in humans: evidence of convergence of cervical afferences on trigeminal nuclei. Cephalalgia. 2001;21(2):107-9.
62. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain. 2005;118(1-2):92-6.
63. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2011;10(10):891-7.
64. Gantenbein AR, Lutz NJ, Riederer F, Sandor PS. Efficacy and safety of 121 injections of the greater occipital nerve in episodic and chronic cluster headache. Cephalalgia. 2012;32(8):630-4.
65. Lambru G, Abu Bakar N, Stahlhut L, McCulloch S, Miller S, Shanahan P, et al. Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. European Journal of Neurology. 2013.
66. Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain. 2013;14(1):86.
67. Pedersen JL, Barloese M, Jensen RH. Neurostimulation in cluster headache: a review of current progress. Cephalalgia. 2013;33(14):1179-93.
68. Jurgens TP, Leone M. Pearls and pitfalls: neurostimulation in headache. Cephalalgia. 2013;33(8):512-25.
69. Leone M, Franzini A, Proietti Cecchini A, Bussone G. Success, failure, and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. Pain. 2013;154(1):89-94.
70. Antoniades CA, Altham PM, Mason SL, Barker RA, Carpenter R. Saccadometry: a new tool for evaluating presymptomatic Huntington patients. Neuroreport. 2007;18(11):1133-6.
71. Robert MPA, Nachev PC, Hicks SL, Golding CVP, Tabrizi SJ, Kennard C. Saccadometry of Conditional Rules in Presymptomatic Huntington's Disease. Annals of the New York Academy of Sciences. 2009;1164(1):444-50.
72. Temel Y, Visser-Vandewalle V, Carpenter RHS. Saccadometry: A novel clinical tool for quantification of the motor effects of subthalamic nucleus stimulation in Parkinson's disease. Experimental Neurology. 2009;216(2):481-9.
73. Barker RA, Michell AW. "The eyes have it". Saccadometry and Parkinson's disease. Experimental Neurology. 2009;219(2):382-4.
74. Carpenter RHS. The saccadic system: a neurological microcosm. Advances in Clinical Neuroscience and Rehabilitation. 2004(4):6-8.
75. Chandna A, Chandrasekharan DP, Ramesh AV, Carpenter R. Altered interictal saccadic reaction time in migraine: a cross-sectional study. Cephalalgia. 2012;32(6):473-80.
76. Carpenter RHS, Williams MLL. Neural computation of log likelihood in control of saccadic eye movements. Nature. 1995;377(6544):59-62.

77. Reddi BAJ, Asrress KN, Carpenter RHS. Accuracy, Information, and Response Time in a Saccadic Decision Task. Journal of Neurophysiology. 2003;90(5):3538-46.
78. Cambron M, Anseeuw S, Paemeleire K, Crevits L. Saccade behaviour in migraine patients. Cephalalgia. 2011;31(9):1005-14.
79. Wilkinson F, Karanovic O, Ross E, Lillakas L, Steinbach M. Ocular Motor Measures in Migraine with and Without Aura. Cephalalgia. 2006;26(6):660-71.
80. Wieser T, Wolff R, Hoffmann KP, Schulte-Mattler W, Zierz S. Persistent ocular motor disturbances in migraine without aura. Neurol Sci. 2004;25(1):8-12.
81. Matharu M. Cluster headache. Clin Evid (Online). 2010.
82. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36.
83. Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. J Headache Pain. 2013;14(1):1.
84. Bakas T, McLennon SM, Carpenter JS, Buelow JM, Otte JL, Hanna KM, et al. Systematic review of health-related quality of life models. Health Qual Life Outcomes. 2012;10:134.
85. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273(1):59-65.
86. Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual model of health-related quality of life. J Nurs Scholarsh. 2005;37(4):336-42.
87. McDougall J, Wright V, Rosenbaum P. The ICF model of functioning and disability: incorporating quality of life and human development. Dev Neurorehabil. 2010;13(3):204-11.
88. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. BMJ. 2001;322(7297):1297-300.
89. Leplège A, Hunt S. The problem of quality of life in medicine. JAMA. 1997;278(1):47-50.
90. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. CMAJ. 1986;134(8):889-95.
91. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.
92. Dijkers M. Measuring quality of life: methodological issues. Am J Phys Med Rehabil. 1999;78(3):286-300.
93. Levy MJ, Matharu M, Goadsby PJ. Chronic headache and pituitary tumors. Curr Pain Headache Rep. 2008;12(1):74-8.
94. Ware Jr JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. Journal of Clinical Epidemiology. 1998;51(11):903-12.
95. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. Journal of the Royal College of General Practitioners. 1985;35(273):185-8.
96. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine. 2001;33(5):337-43.
97. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
98. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.

99. Wagner TH, Patrick DL, Galer BS, Berzon RA. A New Instrument to Assess the Long-term Quality of Life Effects From Migraine: Development and Psychometric Testing of the MSQOL. Headache: The Journal of Head and Face Pain. 1996;36(8):484-92.
100. Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. Headache. 1998;38(4):295-302.
101. Martin BC, Pathak DS, Sharfman MI, Adelman JU, Taylor F, Kwong WJ, et al. Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). Headache. 2000;40(3):204-15.
102. Hartmaier SL, Santanello NC, Epstein RS, Silberstein SD. Development of a Brief 24-Hour Migraine-Specific Quality of Life Questionnaire. Headache: The Journal of Head and Face Pain. 1995;35(6):320-9.
103. Patrick DL, Hurst BC, Hughes J. Further development and testing of the migraine-specific quality of life (MSQOL) measure. Headache. 2000;40(7):550-60.
104. Hambrick JP, Turk CL, Heimberg RG, Schneier FR, Liebowitz MR. The experience of disability and quality of life in social anxiety disorder. Depress Anxiety. 2003;18(1):46-50.
105. Durham CF, Alden KR, Dalton JA, Carlson J, Miller DW, Englebardt SP, et al. Quality of Life and Productivity in Nurses Reporting Migraine. Headache: The Journal of Head and Face Pain. 1998;38(6):427-35.
106. Michel P, Dartigues JF, Lindoulsi A, Henry P. Loss of productivity and quality of life in migraine sufferers among French workers: results from the GAZEL cohort. Headache. 1997;37(2):71-8.
107. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. Neurology. 2000;55(5):624-9.
108. Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF. Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. Cephalalgia. 2003;23(6):441-50.
109. Sharma K, Remanan R, Singh S. Quality of life and psychiatric comorbidity in Indian migraine patients: A headache clinic sample. Neurol India. 2013;61(4):355-9.
110. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression: a population-based case-control study. Neurology. 2000;55(5):629-35.
111. Nicodemo M, Vignatelli L, Grimaldi D, Sancisi E, Fares JE, Zanigni S, et al. Quality of life, eating and mood disorders in menstrual migraine: a case-control study. Neurological Sciences. 2008;29 Suppl 1:S155-7.
112. Osterhaus JT, Townsend RJ, Gandek B, Ware JE. Measuring the Functional Status and Well-Being of Patients with Migraine Headache. Headache: The Journal of Head and Face Pain. 1994;34(6):337-43.
113. Leonardi M, Raggi A, Bussone G, D'Amico D. Health-related quality of life, disability and severity of disease in patients with migraine attending to a specialty headache center. Headache. 2010;50(10):1576-86.
114. Raggi A, Leonardi M, Giovannetti A, Curone M, Bussone G, D'Amico D. A longitudinal evaluation of changes in disability and quality of life in a sample of women with migraine. Neurol Sci. 2011;32 Suppl 1:S189-91.
115. Lantéri-Minet M, Radat F, Chautard M-H, Lucas C. Anxiety and depression associated with migraine: Influence on migraine subjects' disability and quality of life, and acute migraine management. Pain. 2005;118(3):319-26.

116. Paschoal JK, Lin J, Pinho RS, Andreoni S, Minett TS, Vitalle MS, et al. Psychiatric symptoms may contribute to poor quality of life in adolescents with migraine. Pediatr Int. 2013.
117. Stuginski-Barbosa J, Dach F, Bigal M, Speciali JG. Chronic pain and depression in the quality of life of women with migraine--a controlled study. Headache. 2012;52(3):400-8.
118. Zandifar A, Masjedi SS, Haghdoost F, Asgari F, Manouchehri N, Banihashemi M, et al. The psychometric properties of the persian migraine-specific quality of life questionnaire version 2.1 in episodic and chronic migraines. ScientificWorldJournal. 2013;2013:950245.
119. Uthaikhup S, Sterling M, Jull G. Psychological, cognitive and quality of life features in the elderly with chronic headache. Gerontology. 2009;55(6):683-93.
120. Zandifar A, Masjedi SS, Haghdoost F, Asgari F, Manouchehri N, Banihashemi M, et al. The psychometric properties of the persian migraine-specific quality of life questionnaire version 2.1 in episodic and chronic migraines. Scientific World Journal. 2013;vol 2013.
121. Raggi A, Leonardi M, Ajovalasit D, D'Amico D, Bussone G. Disability and functional profiles of patients with migraine measured with ICF classification. International Journal of Rehabilitation Research. 2010;33(3):225-31.
122. Leonardi M, Raggi A, Ajovalasit D, Bussone G, D'Amico D. Functioning and disability in migraine. Disability and Rehabilitation. 2010;32 Suppl 1:S23-32.
123. Ruiz de Velasco I, Gonzalez N, Etxeberria Y, Garcia-Monco JC. Quality of life in migraine patients: a qualitative study. Cephalalgia. 2003;23(9):892-900.
124. D'Amico D, Genco S, Perini F. Workplace disability in migraine: an Italian experience. Neurol Sci. 2004;25 Suppl 3:S251-2.
125. Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. Canadian Journal of Neurological Sciences. 2012;39(2 Suppl 2):S1-59.
126. Raggi A, Leonardi M, Bussone G, D'Amico D. Value and utility of disease-specific and generic instruments for assessing disability in patients with migraine, and their relationships with health-related quality of life. Neurol Sci. 2011;32(3):387-92.
127. Gedikoglu U, Coskun O, Inan LE, Ucler S, Tunc T, Emre U. Validity and reliability of Turkish translation of Migraine Disability Assessment (MIDAS) questionnaire in patients with migraine. Cephalalgia. 2005;25(6):452-6.
128. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. Cephalalgia. 1999;19(2):107-14; discussion 74.
129. D'Amico D, Mosconi P, Genco S, Usai S, Prudenzano AM, Grazzi L, et al. The Migraine Disability Assessment (MIDAS) questionnaire: translation and reliability of the Italian version. Cephalalgia. 2001;21(10):947-52.
130. Park JW, Shin HE, Kim JS, Lee KS. Assessing migraine disability by diary-based measurement: relationship to the characteristics of individual headache attacks. European Journal of Neurology. 2008;15(8):817-21.
131. Juyal R, Verma R, Garg RK, Shukla R, Agarwal A, Singh MK. Reliability and validity of Hindi translation of the migraine disability assessment and headache impact test-6 questionnaires. Ann Indian Acad Neurol. 2010;13(4):276-83.
132. Wahab KW, Ugheoke AJ. Migraine: prevalence and associated disability among Nigerian undergraduates. Canadian Journal of Neurological Sciences. 2009;36(2):216-21.

133. Kim BK, Chung YK, Kim JM, Lee KS, Chu MK. Prevalence, clinical characteristics and disability of migraine and probable migraine: a nationwide population-based survey in Korea. Cephalalgia. 2013;33(13):1106-16.
134. Ford S, Calhoun A, Kahn K, Mann J, Finkel A. Predictors of disability in migraineurs referred to a tertiary clinic: neck pain, headache characteristics, and coping behaviors. Headache. 2008;48(4):523-8.
135. Nachit-Ouinekh F, Dartigues JF, Henry P, Becg JP, Chastan G, Lemaire N, et al. Use of the headache impact test (HIT-6) in general practice: relationship with quality of life and severity. European Journal of Neurology. 2005;12(3):189-93.
136. Kolotylo CJ, Broome ME. Predicting disability and quality of life in a community-based sample of women with migraine headache. Pain Manag Nurs. 2000;1(4):139-51.
137. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. Neurology. 2006;67(1):109-13.
138. Schwedt TJ, Matharu MS, Dodick DW. Thunderclap headache. Lancet Neurol. 2006;5(7):621-31.
139. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Archives of Internal Medicine. 1999;159(8):813-8.
140. Fagan MA. Exploring the relationship between maternal migraine and child functioning. Headache. 2003;43(10):1042-8.
141. Powers SW, Patton SR, Hommel KA, Hershey AD. Quality of life in paediatric migraine: characterization of age-related effects using PedsQL 4.0. Cephalalgia. 2004;24(2):120-7.
142. Kashikar-Zuck S, Zafar M, Barnett KA, Aylward BS, Strotman D, Slater SK, et al. Quality of life and emotional functioning in youth with chronic migraine and juvenile fibromyalgia. Clinical Journal of Pain. 2013;29(12):1066-72.
143. Tkachuk GA, Cottrell CK, Gibson JS, O'Donnell FJ, Holroyd KA. Factors associated with migraine-related quality of life and disability in adolescents: a preliminary investigation. Headache. 2003;43(9):950-5.
144. Frare M, Axia G, Battistella PA. Quality of Life, Coping Strategies, and Family Routines in Children with Headache. Headache: The Journal of Head and Face Pain. 2002;42(10):953-62.
145. Palermo TM, Putnam J, Armstrong G, Daily S. Adolescent autonomy and family functioning are associated with headache-related disability. Clinical Journal of Pain. 2007;23(5):458-65.
146. Blumenfeld A, Varon S, Wilcox T, Buse D, Kawata A, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011;31(3):301-15.
147. Saunders K, Merikangas K, Low NC, Von Korff M, Kessler RC. Impact of comorbidity on headache-related disability. Neurology. 2008;70(7):538-47.
148. Dahlöf C, Dimenäs E. Migraine Patients Experience Poorer Subjective Well-Being/Quality of Life Even Between Attacks. Cephalalgia. 1995;15(1):31-6.
149. Holroyd KA, Drew JB, Cottrell CK, Romanek KM, Heh V. Impaired functioning and quality of life in severe migraine: the role of catastrophizing and associated symptoms. Cephalalgia. 2007;27(10):1156-65.
150. Mula M, Viana M, Jauch R, Schmitz B, Bettucci D, Cavanna AE, et al. Health-related quality of life measures and psychiatric comorbidity in patients with migraine. European Journal of Neurology. 2009;16(9):1017-21.

151. Kolotylo CJ, Broome ME. Exploration of migraine pain, disability, depressive symptomatology, and coping: a pilot study. Health Care for Women International. 2000;21(3):203-18.
152. Bruijn J, Arts WF, Duivenvoorden H, Dijkstra N, Raat H, Passchier J. Quality of life in children with primary headache in a general hospital. Cephalalgia. 2009;29(6):624-30.
153. Bigal ME, Bigal JM, Betti M, Bordini CA, Speciali JG. Evaluation of the impact of migraine and episodic tension-type headache on the quality of life and performance of a university student population. Headache. 2001;41(7):710-9.
154. Milde-Busch A, Heinrich S, Thomas S, Kuhnlein A, Radon K, Straube A, et al. Quality of life in adolescents with headache: results from a population-based survey. Cephalalgia. 2010;30(6):713-21.
155. Nodari E, Battistella PA, Naccarella C, Vidi M. Quality of life in young Italian patients with primary headache. Headache. 2002;42(4):268-74.
156. Morelli N, Rota E, Gori S, Guidetti D, Michieletti E, De Simone R, et al. Brainstem activation in cluster headache: an adaptive behavioural response? Cephalalgia. 2013;33(6):416-20.
157. Holroyd KA, Stensland M, Lipchik GL, Hill KR, O'Donnell FS, Cordingley G. Psychosocial Correlates and Impact of Chronic Tension-type Headaches. Headache: The Journal of Head and Face Pain. 2000;40(1):3-16.
158. Silva HM, Jr., Garbelini RP, Teixeira SO, Bordini CA, Speciali JG. Effect of episodic tension-type headache on the health-related quality of life in employees of a Brazilian public hospital. Arquivos de Neuro-Psiquiatria. 2004;62(3B):769-73.
159. Bagley CL, Rendas-Baum R, Maglinte GA, Yang M, Varon SF, Lee J, et al. Validating Migraine-Specific Quality of Life Questionnaire v2.1 in episodic and chronic migraine. Headache. 2012;52(3):409-21.
160. Penacoba-Puente C, Fernandez-de-Las-Penas C, Gonzalez-Gutierrez JL, Miangolarra-Page JC, Pareja JA. Interaction between anxiety, depression, quality of life and clinical parameters in chronic tension-type headache. Eur J Pain. 2008;12(7):886-94.
161. Jürgens TP, Gaul C, Lindwurm A, Dresler T, Paelecke-Habermann Y, Schmidt-Wilcke T, et al. Impairment in episodic and chronic cluster headache. Cephalalgia. 2011;31(6):671-82.
162. D'Amico D, Rigamonti A, Solari A, Leone M, Usai S, Grazzi L, et al. Health-related quality of life in patients with cluster headache during active periods. Cephalalgia. 2002;22(10):818-21.
163. Jensen RM, Lyngberg A, Jensen RH. Burden of cluster headache. Cephalalgia. 2007;27(6):535-41.
164. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Geraud G, et al. Chronic cluster headache: a French clinical descriptive study. Journal of neurology, neurosurgery, and psychiatry. 2007;78(12):1354-8.
165. Duru G, Auray J-P, Gaudin A-F, Dartigues J-F, Henry P, Lanteri-Minet M, et al. Impact of headache on quality of life in a general population survey in France (GRIM2000 Study). Headache. 2004;44(6):571-80.
166. Cavallini A, Micieli G, Bussone G, Rossi F, Nappi G. Headache and quality of life. Headache. 1995;35(1):29-35.
167. D'Amico D, Usai S, Grazzi L, Rigamonti A, Solari A, Leone M, et al. Quality of life and disability in primary chronic daily headaches. Neurological Sciences. 2003;24(0):s97-s100.

168. Canuet L, Ishii R, Fernandez-Concepcion O, Iwase M, Takeda M. Severity of depressive symptoms as predictor of impairment of quality of life in chronic migraine: Comparison with episodic migraine. Psychiatry and Clinical Neurosciences. 2008;62(6):738-40.
169. Stewart WF, Lipton RB, Simon D. Work-related disability: results from the American migraine study. Cephalalgia. 1996;16(4):231-8; discussion 15.
170. El Hasnaoui A, Vray M, Blin P, Nachit-Ouinekh F, Boureau F. Assessment of migraine severity using the MIGSEV scale: relationship to migraine features and quality of life. Cephalalgia. 2004;24(4):262-70.
171. Fuh JL, Wang SJ, Lu SR, Liao YC, Chen SP, Yang CY. Headache disability among adolescents: a student population-based study. Headache. 2010;50(2):210-8.
172. Kaczynski KJ, Claar RL, Lebel AA. Relations between pain characteristics, child and parent variables, and school functioning in adolescents with chronic headache: a comparison of tension-type headache and migraine. Journal of Pediatric Psychology. 2013;38(4):351-64.
173. Shin HE, Park JW, Kim YI, Lee KS. Headache Impact Test-6 (HIT-6) scores for migraine patients: Their relation to disability as measured from a headache diary. J Clin Neurol. 2008;4(4):158-63.
174. Fuh JL, Wang SJ. Comparison of Short Form-36 and Migraine Disability Assessment questionnaire in patients with migraine. Clinical Journal of Pain. 2006;22(6):564-8.
175. Dando WE, Branch MA, Maye JP. Headache disability in orofacial pain patients. Headache. 2006;46(2):322-6.
176. Villani V, Prosperini L, Pozzilli C, Salvetti M, Sette G. Quality of life of multiple sclerosis patients with comorbid migraine. Neurol Sci. 2011;32 Suppl 1:S149-51.
177. Passchier J, de Boo M, Quaak HZ, Brienen JA. Health-related quality of life of chronic headache patients is predicted by the emotional component of their pain. Headache. 1996;36(9):556-60.
178. Branch MA. Headache disability in orofacial pain patients is related to traumatic life events. Headache. 2009;49(4):535-40.
179. Kroner-Herwig B, Heinrich M, Vath N. The assessment of disability in children and adolescents with headache: adopting PedMIDAS in an epidemiological study. Eur J Pain. 2010;14(9):951-8.
180. Sokolovic E, Riederer F, Szucs T, Agosti R, Sandor PS. Self-reported headache among the employees of a Swiss university hospital: prevalence, disability, current treatment, and economic impact. J Headache Pain. 2013;14(1):29.
181. Micieli G, Frediani F, Cavallini A, Rossi F, Bussone G, Merli S, et al. Quantification of headache disability: a diagnostic-based approach. Headache. 1995;35(3):131-7.
182. Gedikoglu U, Ucler S, Inan LE, Coskun O, Tunc T. A preliminary study: validity and reliability of Turkish translation of migraine disability assessment (MIDAS) questionnaire in Turkish patients with chronic tension type headache. International Journal of Neuroscience. 2006;116(11):1337-45.
183. Vadikolias K, Heliopoulos I, Tripsianis G, Achtaropoulos A, Homsioglou E, Artemis N, et al. Headache-related work disability in young men. The Journal of Headache and Pain. 2002;3(2):87-91.
184. D'Amico D, Bussone G. Disability and migraine: recent outcomes using an Italian version of MIDAS. J Headache Pain. 2003;4 (Suppl 1):S42-S6.

185. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001;412(6843):150-7.
186. Huettel SA, Song AW, McCarthy G. Functional Magnetic Resonance Imaging. Second ed. Sunderland, Massachusetts U.S.A.: Sinauer Associates, Inc; 2008.
187. Detre JA, Wang J, Wang Z, Rao H. Arterial spin-labeled perfusion MRI in basic and clinical neuroscience. Curr Opin Neurol. 2009;22(4):348-55.
188. Aguirre GK, Detre JA, Wang J. Perfusion fMRI for functional neuroimaging. Int Rev Neurobiol. 2005;66:213-36.
189. Detre JA, Wang J. Technical aspects and utility of fMRI using BOLD and ASL. Clin Neurophysiol. 2002;113(5):621-34.
190. Murphy SE, Mackay CE. Using MRI to measure drug action: caveats and new directions. J Psychopharmacol. 2011;25(9):1168-74.
191. Chen Y, Wan HI, O'Reardon JP, Wang DJ, Wang Z, Korczykowski M, et al. Quantification of cerebral blood flow as biomarker of drug effect: arterial spin labeling phMRI after a single dose of oral citalopram. Clin Pharmacol Ther. 2011;89(2):251-8.
192. Bruns A, Künnecke B, Risterucci C, Moreau JL, von Kienlin M. Validation of cerebral blood perfusion imaging as a modality for quantitative pharmacological MRI in rats. Magn Reson Med. 2009;61(6):1451-8.
193. Petersen ET, Zimine I, Ho YC, Golay X. Non-invasive measurement of perfusion: a critical review of arterial spin labelling techniques. Br J Radiol. 2006;79(944):688-701.
194. Hodkinson DJ, Krause K, Khawaja N, Renton TF, Huggins JP, Vennart W, et al. Quantifying the test-retest reliability of cerebral blood flow measurements in a clinical model of on-going post-surgical pain: A study using pseudo-continuous arterial spin labelling. Neuroimage Clin. 2013;3:301-10.
195. Howard MA, Krause K, Khawaja N, Massat N, Zelaya F, Schumann G, et al. Beyond patient reported pain: perfusion magnetic resonance imaging demonstrates reproducible cerebral representation of ongoing post-surgical pain. PLoS One. 2011;6(2):e17096.
196. Kato Y, Araki N, Matsuda H, Ito Y, Suzuki C. Arterial spin-labeled MRI study of migraine attacks treated with rizatriptan. J Headache Pain. 2010;11(3):255-8.
197. Wasan AD, Loggia ML, Chen LQ, Napadow V, Kong J, Gollub RL. Neural correlates of chronic low back pain measured by arterial spin labeling. Anesthesiology. 2011;115(2):364-74.
198. Owen DG, Bureau Y, Thomas AW, Prato FS, St Lawrence KS. Quantification of pain-induced changes in cerebral blood flow by perfusion MRI. Pain. 2008;136(1-2):85-96.
199. Williams DS. Quantitative perfusion imaging using arterial spin labeling. Methods Mol Med. 2006;124:151-73.
200. Wolf RL, Detre JA. Clinical neuroimaging using arterial spin-labeled perfusion magnetic resonance imaging. Neurotherapeutics. 2007;4(3):346-59.
201. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med. 2008;60(6):1488-97.
202. Teepker M, Peters M, Vedder H, Schepelmann K, Lautenbacher S. Menstrual variation in experimental pain: correlation with gonadal hormones. Neuropsychobiology. 2010;61(3):131-40.

203. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1(3):277-99.
204. McLafferty E, Farley A. Assessing pain in patients. Nurs Stand. 2008;22(25):42-6.
205. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.
206. Marlow RA, Kegowicz CL, Starkey KN. Prevalence of Depression Symptoms in Outpatients with a Complaint of Headache. J Am Board Fam Med. 2009;22(6):633-7.
207. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. Journal of Psychosomatic Research. 2002;52(2):69-77.
208. Buenaver LF, Edwards RR, Smith MT, Gramling SE, Haythornthwaite JA. Catastrophizing and pain-coping in young adults: associations with depressive symptoms and headache pain. J Pain. 2008;9(4):311-9.
209. Stewart MW, Harvey ST, Evans IM. Coping and catastrophizing in chronic pain: a psychometric analysis and comparison of two measures. J Clin Psychol. 2001;57(1):131-8.
210. Autret A, Roux S, Rimbaux-Lepage S, Valade D, Debiais S. Psychopathology and quality of life burden in chronic daily headache: influence of migraine symptoms. J Headache Pain. 2010;11(3):247-53.
211. Goretti B, Portaccio E, Zipoli V, Hakiki B, Siracusa G, Sorbi S, et al. Coping strategies, psychological variables and their relationship with quality of life in multiple sclerosis. Neurological Sciences. 2009;30(1):15-20.
212. Smillie LD, Bhairo Y, Gray J, Gunasinghe C, Elkin A, McGuffin P, et al. Personality and the bipolar spectrum: normative and classification data for the Eysenck Personality Questionnaire-Revised. Comprehensive Psychiatry.50(1):48-53.
213. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6) across episodic and chronic migraine. Cephalalgia. 2011;31(3):357-67.
214. Duvernoy HM, Bourgouin P. The human brain : surface, three-dimensional sectional anatomy with MRI, and blood supply. 2nd ed. Wien u.a.: Springer; 1999. 491 p.
215. Naidich TP, Duvernoy HM. Duvernoy's atlas of the human brain stem and cerebellum : high-field MRI : surface anatomy, internal structure, vascularization and 3D sectional anatomy. Wien ; New York: Springer; 2009. 876 p.
216. Iacovelli E, Coppola G, Tinelli E, Pierelli F, Bianco F. Neuroimaging in cluster headache and other trigeminal autonomic cephalalgias. The Journal of Headache and Pain. 2012;13(1):11-20.
217. Magis D, Bruno MA, Fumal A, Gerardy PY, Hustinx R, Laureys S, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. BMC Neurol. 2011;11:25.
218. Davies P. What has imaging taught us about migraine? Maturitas. 2011;70(1):34-6.
219. Colombo B, Dalla Costa G, Dalla Libera D, Comi G. From neuroimaging to clinical setting: what have we learned from migraine pain? Neurol Sci. 2012;33 Suppl 1:S95-7.

220. Auer T, Janszky J, Schwarcz A, Dóczi T, Trauninger A, Alkonyi B, et al. Attack-related brainstem activation in a patient with SUNCT syndrome: an ictal fMRI study. Headache. 2009;49(6):909-12.
221. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. Mol Pain. 2010;6:27.
222. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain. 1995;60(1):3-38.
223. Maleki N, Becerra L, Nutile L, Pendse G, Brawn J, Bigal M, et al. Migraine attacks the Basal Ganglia. Mol Pain. 2011;7:71.
224. Kobari M, Meyer JS, Ichijo M, Imai A, Oravez WT. Hyperperfusion of cerebral cortex, thalamus and basal ganglia during spontaneously occurring migraine headaches. Headache. 1989;29(5):282-9.
225. Yuan K, Zhao L, Cheng P, Yu D, Dong T, Xing L, et al. Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. J Pain. 2013;14(8):836-44.
226. Schmitz N, Admiraal-Behloul F, Arkink EB, Kruit MC, Schoonman GG, Ferrari MD, et al. Attack frequency and disease duration as indicators for brain damage in migraine. Headache. 2008;48(7):1044-55.
227. Ossemann M. Recurrence of cluster headache with pramipexole. Acta Neurol Belg. 2010;110(3):279-80.
228. Rozen TD. Olanzapine as an abortive agent for cluster headache. Headache. 2001;41(8):813-6.
229. Datta SS, Kumar S. Clozapine-responsive cluster headache. Neurol India. 2006;54(2):200-1.
230. Caviness VS, O'Brien P. Cluster headache: response to chlorpromazine. Headache. 1980;20(3):128-31.
231. D'Andrea G, Granella F, Perini F, Farruggio A, Leone M, Bussone G. Platelet levels of dopamine are increased in migraine and cluster headache. Headache. 2006;46(4):585-91.
232. Waldenlind E, Gustafsson SA. Prolactin in cluster headache: diurnal secretion, response to thyrotropin-releasing hormone, and relation to sex steroids and gonadotropins. Cephalalgia. 1987;7(1):43-54.
233. Lepper A, Frese A, Summ O, Nofer JR, Evers S. Hypothalamic dopaminergic stimulation in cluster headache. Cephalalgia. 2013;33(14):1155-9.
234. Lambru G, Matharu M. Traumatic head injury in cluster headache: cause or effect? Curr Pain Headache Rep. 2012;16(2):162-9.
235. Davis KD, Moayedi M. Central mechanisms of pain revealed through functional and structural MRI. J Neuroimmune Pharmacol. 2013;8(3):518-34.
236. Davis KD. Neuroimaging of pain: what does it tell us? Curr Opin Support Palliat Care. 2011;5(2):116-21.
237. Legrain V, Iannetti GD, Plaghki L, Mouraux A. The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol. 2011;93(1):111-24.
238. May A. Chronic pain may change the structure of the brain. Pain. 2008;137(1):7-15.
239. Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci. 2005;28:377-401.
240. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain. 2009;10(11):1113-20.

241. Apkarian AV. The brain in chronic pain: clinical implications. Pain Manag. 2011;1(6):577-86.
242. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Prog Neurobiol. 2009;87(2):81-97.
243. Seifert F, Maihöfner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. Cell Mol Life Sci. 2009;66(3):375-90.
244. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology. 2003;61(12):1707-15.
245. Naegel S, Holle D, Obermann M. Structural imaging in cluster headache. Curr Pain Headache Rep. 2014;18(5):415.
246. Matharu MS, Cohen AS, Frackowiak RSJ, Goadsby PJ. Posterior hypothalamic activation in paroxysmal hemicrania. Annals of Neurology. 2006;59(3):535-45.
247. Gwilym SE, Filippini N, Douaud G, Carr AJ, Tracey I. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. Arthritis Rheum. 2010;62(10):2930-40.
248. Wu MT, Sheen JM, Chuang KH, Yang P, Chin SL, Tsai CY, et al. Neuronal specificity of acupuncture response: a fMRI study with electroacupuncture. Neuroimage. 2002;16(4):1028-37.
249. Nouraei SA, De Pennington N, Jones JG, Carpenter RH. Dose-related effect of sevoflurane sedation on higher control of eye movements and decision making. Br J Anaesth. 2003;91(2):175-83.
250. Terao Y, Fukuda H, Ugawa Y, Hikosaka O. New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: a clinical review. Clin Neurophysiol. 2013;124(8):1491-506.
251. Hikosaka O, Takikawa Y, Kawagoe R. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol Rev. 2000;80(3):953-78.
252. Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. Science. 1999;283(5401):549-54.
253. D'Andrea G, Perini F, Granella F, Cananzi A, Sergi A. Efficacy of transdermal clonidine in short-term treatment of cluster headache: a pilot study. Cephalalgia. 1995;15(5):430-3.
254. Leone M, Attanasio A, Grazzi L, Libro G, D'Amico D, Moschiano F, et al. Transdermal clonidine in the prophylaxis of episodic cluster headache: an open study. Headache. 1997;37(9):559-60.
255. D'Alessandro R. Tizanidine for chronic cluster headache. Arch Neurol. 1996;53(11):1093.
256. D'Andrea G, Cananzi AR, Morra M, Martignoni E, Fornasiero S, Zamberlan F, et al. Platelet catecholamines in cluster headache. J Neurol Neurosurg Psychiatry. 1992;55(4):308-9.
257. van Stockum S, MacAskill MR, Anderson TJ. Impairment of voluntary saccades and facilitation of reflexive saccades do not co-occur in Parkinson's disease. J Clin Neurosci. 2012;19(8):1119-24.
258. Bussone G, Usai S, Grazzi L, Rigamonti A, Solari A, D'Amico D. Disability and quality of life in different primary headaches: results from Italian studies. Neurological Sciences. 2004;25(0):s105-s7.

259. Cavanna AE, Schrag A, Morley D, Orth M, Robertson MM, Joyce E, et al. The Gilles de la Tourette syndrome-quality of life scale (GTS-QOL): development and validation. Neurology. 2008;71(18):1410-6.
260. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Quality of Life Research. 1995;4(3):241-8.
261. Ferketich S. Focus on psychometrics. Aspects of item analysis. Res Nurs Health. 1991;14(2):165-8.
262. Rattray J, Jones MC. Essential elements of questionnaire design and development. J Clin Nurs. 2007;16(2):234-43.
263. Boyle G. Does item homogeneity indicate internal consistency or item redundancy in psychometric scales? Person individ Diff. 1991;12(3):291-4.
264. Field AP. Discovering statistics using SPSS. Los Angeles, [Calif.]; London: SAGE; 2009.
265. Cronbach L. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334.
266. Fayers PM, Hand DJ. Factor analysis, causal indicators and quality of life. Quality of Life Research. 1997;6(2):139-50.
267. Velicer W, Fava J. Affects of variable and subject sampling on factor pattern recovery. 1998;3:231-51.
268. Ware JE. Standards for validating health measures: definition and content. J Chronic Dis. 1987;40(6):473-80.
269. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology. 2001;56(6 Suppl 1):S20-8.
270. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Jr., Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Quality of Life Research. 2003;12(8):963-74.
271. Jacobson GP, Ramadan NM, Aggarwal SK, Newman CW. The Henry Ford Hospital Headache Disability Inventory (HDI). Neurology. 1994;44(5):837-42.
272. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983;67(6):361-70.
273. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. Journal of Neuropsychiatry and Clinical Neurosciences. 1992;4(2):134-9.
274. Steed L. Further Validity and Reliability Evidence for Beck Hopelessness Scale Scores in a Nonclinical Sample. Educational and Psychological Measurement. 2001;61(2):303-16.
275. Jackson C. The General Health Questionnaire. Occupational Medicine. 2007;57(1):79.
276. Philips HC, Jahanshahi M. The components of pain behaviour report. Behav Res Ther. 1986;24(2):117-25.
277. Wongpakaran T, Tinakon W, Wongpakaran N, Nahathai W. A comparison of reliability and construct validity between the original and revised versions of the Rosenberg Self-Esteem Scale. Psychiatry Investig. 2012;9(1):54-8.
278. Jahanshahi M, Marsden CD. Personality in torticollis: a controlled study. Psychol Med. 1988;18(2):375-87.
279. Sarason I, Levine H, Basham R, Sarason B. Assessing social support: the social support questionnaire J Pers Soc Psychol 1983;44:127-39.

280. Felton BJ, Revenson TA, Hinrichsen GA. Stress and coping in the explanation of psychological adjustment among chronically ill adults. Soc Sci Med. 1984;18(10):889-98.
281. MacDonald LD, Anderson HR. Stigma in patients with rectal cancer: a community study. J Epidemiol Community Health. 1984;38(4):284-90.
282. Bahra A, Goadsby PJ. Diagnostic delays and mis-management in cluster headache. Acta Neurologica Scandinavica. 2004;109(3):175-9.
283. Bittar G, Graff-Radford SB. A retrospective study of patients with cluster headaches. Oral Surgery, Oral Medicine, Oral Pathology. 1992;73(5):519-25.
284. Raimondi E. Premonitory symptoms in cluster headache. Curr Pain Headache Rep. 2001;5(1):55-9.
285. Blau JN, Engel HO. Premonitory and prodromal symptoms in cluster headache. Cephalalgia. 1998;18(2):91-3; discussion 71-2.
286. Seifert CL, Valet M, Pfaffenrath V, Boecker H, Ruther KV, Tolle TR, et al. Neurometabolic correlates of depression and disability in episodic cluster headache. Journal of Neurology. 2011;258(1):123-31.
287. Sanchez del Rio M, Alvarez Linera J. Functional neuroimaging of headaches. Lancet Neurol. 2004;3(11):645-51.
288. Sprenger T, Ruether KV, Boecker H, Valet M, Berthele A, Pfaffenrath V, et al. Altered metabolism in frontal brain circuits in cluster headache. Cephalalgia. 2007;27(9):1033-42.

APPENDIX A: Quality of life booklet of questionnaires

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17 October 2011

The aim of this booklet of questionnaires is to evaluate the effect of your cluster headaches on you and your daily life. Please first read the information sheet describing the aims of the study and your rights. After reading the information sheet if you are willing to help us and participate in the survey, please sign the consent form before completing the rest of the booklet.

Some of the questions in this booklet are about the physical effects of the illness. The majority of the questions are, however, about the personal and emotional effects of the illness on you. When completing the forms, please remember that there are no right or wrong answers and that we are simply interested in your personal views and experiences in coping with your cluster headaches. All the information that you provide will be strictly confidential and will not be used in any way other than for research purposes. Our final research report will be concerned with information from a group of people with cluster headaches and the information provided by any individual person will not be identifiable. Please answer all the questions on each form. When completed, please return the booklet in the stamped, addressed envelope provided.

We are most grateful to you for your help.

Dr Manjit Matharu

Professor Marjan Jahanshahi

University College London Hospitals NHS
NHS Trust

The National Hospital for Neurology and Neurosurgery
Institute of Neurology
Sobell Department of Motor Neuroscience and Movement Disorders
8/11 Queen Square
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Date: 1/4/2010 Version 1

Patient information sheet

Confidential

Study Title: Development and Validation of a new Cluster Headache (CH) quality of life (QoL) Scale: CH-QoL- A pilot Study

You are invited to participate in a research study conducted at the Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Before you decide whether you wish to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Aims of the Study:

The purpose of the study is to develop and validate a scale that is unique in measuring the quality of life of people with cluster headache. In the past, the quality of life of people with cluster headache was measured using generic scales used to asses quality of life in the general population or scales developed specifically for other types of headache such as Migraine. However, the nature, distribution, frequency and severity of pain in cluster headaches is very different from other types of headaches and is likely to have a very distinct impact on quality of life of sufferers. Therefore, use of scales developed for other types of headache to measure quality of life is not ideal. The aim of this study is to develop a new and disease-specific measure of quality of life for use with people who suffer from cluster headache. Such a cluster headache quality of life scale (CH-QoL) would be of value for assessing the impact of various forms of treatment on the quality of life of people with cluster headache.

Why have you been invited to participate in the study?

You have been invited to participate because you suffer from cluster headache. If you agree to participate you will be one of the 200 to 400 people with cluster headache whom we hope to recruit into the study.

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Do you have to take part?

It is your choice whether or not to participate in the study. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw from the study at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive if you are a patient at The National Hospital.

What we would like you to do during the study

We would like you to answer the questions and fill in the forms in the attached booklet containing a number of different questionnaires which we have sent you in the post with a stamped and addressed envelope for returning the booklet to us when fully completed. These questionnaires tell us about the nature and severity of your cluster headaches and more importantly aspects of your well-being such as depression, levels of social support, ways of coping with cluster headaches, and impact of cluster headaches on your quality of life. The booklet will take approximately 1 hour to complete. Two weeks later we will ask you to complete only one of the questionnaires, the cluster headache quality of life scale, for a second time. This will be sent to you in the post with a stamped, addressed return envelope.

What are the risks and side effects of taking part in the study?

There are no side effects or risks involved in taking part in this study.

A counsellor, Professor Marjan Jahanshahi, will be available on 0203 4488733 to discuss any issues or difficulties that might arise during your participation in the study.

What are the possible benefits?

Participation in this study will not directly give you any benefit. The study will lead to a better understanding of the impact of cluster headache on daily activities and quality of life of people with the disorder. It will lead to development and validation of a CH-QoL scale that can be used to assess the effects of medical and surgical treatments and changes in quality of life in the course of the illness in future. This information will improve our understanding of the impact of the disorder and its medical management.

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What information about me will be held?

We will keep a record of your name, age, address, contact details, and the severity of your cluster headache using rating scales. The results will be stored on a computer for analysis. All information which is collected about you during the course of the study will stay strictly confidential and remain within the Institute of Neurology / UCL. Any information about you which leaves the Institute of Neurology will have your name, address, birth date and all identifiable information removed so that you cannot be recognised from it. Data protection procedures are in place and the principal investigator, Prof. Marjan Jahanshahi, will be in charge of ensuring that the security and confidentiality of your information is maintained. At the end of the study, all the collected data will be stored for 5 years.

What will happen to the results?

The data will be analyzed and submitted for publication in a scientific journal. It should be emphasized that your name or any information that could identify you (e. g your date of birth) will not be published. We will be happy to provide you a copy of the completed article for you to keep.

Can I withdraw from the study?

Your participation in the study is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time, without having to give reason. If you choose not to enter the study or to withdraw once entered, this will not affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will be only used for medical purposes. Your medical records may be inspected by competent authorities and properly authorized persons, but if any information is released, this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

What if something goes wrong?

If you have a specific complaint against your treatment by a member of staff (doctors, nurses, etc) you have the right to complain using the usual UCLH complaints procedure. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this if you wish to complain, or have any concerns for this study, the normal National Health Service complaints mechanisms should be available to you.

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Has the study been approved by an independent body?
The study has been reviewed and given a favourable opinion by the Principal Investigator Ethics Review Panel of the Sobell Department of Motor Neuroscience and Movement Disorders of the Institute of Neurology, as well as the North West London Research Ethics Committee 1.

Where will the study take place?
The study will be completed at the UCL Institute of Neurology and the National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG.

Contacts:
If you are willing to help with this research study or would like to discuss this project further, please contact one of us by phone or email:

Dr Manjit Marathu
UCL Institute of Neurology
33 Queen Square, London WC1N 3BG
m.matharu@uclmail.net

Prof Marjan Jahanshahi (principal investigator)
Sobell Department of Motor Neuroscience and Movement Disorders
Box 146, UCL Institute of Neurology
33 Queen Square
London WC1N 3BG
Phone: 02031080033
m.jahanshahi@ion.ucl.ac.uk

If you agree to take part in the study, you will be given a copy of this information sheet and a signed consent form to keep.

University College London Hospitals NHS
NHS Trust

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Subject Identification Number for this study: 10/H0722/43 Version and date: Version 5 – 1/4/2010

CONSENT FORM - CONFIDENTIAL

Study Title: Development and Validation of a new Cluster Headache (CH) quality of life (QoL) Scale: CH-QoL- A pilot Study

Name of Principal investigator:
Prof. Marjan Jahanshahi

Please initial box

1. I confirm that I have read and understood the information sheet dated 14/02/11..... (version 5.) for the above study and have had the opportunity to ask questions. ☐
2. I confirm that I have had sufficient time to consider whether or not want to be included in the study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from (company name) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the above study. ☐

Continued on next page/

1 form for Patient;
1 to be kept as part of the study documentation,
1 to be kept with hospital notes

University College London Hospitals NHS
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Subject Identification Number for this study: 10/H0722/43 Version and date: Version 5 – 1/4/2010

CONSENT FORM - CONFIDENTIAL

Title of project: Development and Validation of a Cluster Headache (CH) quality of life (QoL) Scale: CH-QoL- A pilot Study

Name of Principal investigator:
Prof Marjan Jahanshahi

Name of patient	Date	Signature

Name of Person taking consent (if different from researcher)	Date	Signature
Dr Manjit Matharu	14/02/11	

Prof Marjan Jahanshahi
Name of the research to contacted if there are any problems

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top this consent form

CH-QoL: Scale Development

Full Name:.....

Address:.....

.....

Telephone:.....

Today's date: .....

Date of Birth:.....

Sex: Male Female

Handedness: Right Left Ambidextrous

Marital Status:

Single Married/Cohabiting

Widowed Divorced/Separated

Present Employment Status:

a) Employed Full-time
b) Employed Part-time
c) Retired early prior to normal retirement age
d) Retired at normal retirement age
e) Unemployed because of disability for more than six months
f) Unemployed temporarily (less than six months) and seeking employment
g) Student
h) Housewife
i) Never employed

Occupation (current or job done for the longest period)

.....

Years of Education: .....
(left school at age: , years of university/college:)

1. **Age at onset of cluster headaches:**

.....

2. **Are you currently having cluster headaches?**

   Yes No

   If you are having cluster headaches currently then when did your current bout start?

   .....

   If you are not having cluster headaches currently, then when was your last cluster headache?

   .....

3. **Over the last year, what was the duration of the longest remission (without drugs)?**

   ( ) No remission

   ( ) < 1 month

   ( ) > 1 month

4. **Side of Cluster Headache**

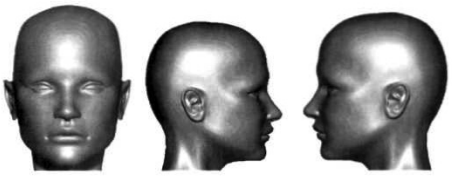
   ( ) Right side only

   ( ) Left side only

   ( ) One-sided headaches but side changes from headache to headache

   ( ) Both sides

5. **Distribution of Cluster Headache (Please mark on diagrams below)**



6. **How long does each headaches episode last when treated with abortive medications?**

.....

7. **How severe are your headache?**

( ) **Mild**

( ) **Moderate**

( ) **Severe**

( ) **Very severe**

( ) **Excruciating**

8. **How many headaches do you generally have daily or weekly?**

.....

9. Which of the following symptoms do you get during a cluster headache?

( ) Redness of the eye **( ) Runny nose**

( ) Watering of the eye **( ) Blocked nose**

( ) Facial sweating **( ) Ear discomfort**

( ) Drooping of eyelid **( ) Facial redness**

( ) Small pupil **( ) Swelling of eye**

( ) Agitation or restlessness

10. Do you experience any nausea or vomiting associated with headaches?

Yes **No**

11. **Do you have any warning symptoms before attack?**

Yes **No**

What was the warning symptoms and how long?

.....

12. Do you suffer from other forms of headaches?

.....

13. Do you smoke? **Yes** **No**

14. Is there anything you can do to improve the pain or shorten the Cluster Headache episode?

.....

.....

.....

.....

15. Medication Type mg/day Number/day

Acute Medication (to cure pain)

.....

.....

.....

.....

.....

Prophylactic (preventive) medication

.....

.....

.....

.....

.....

.....

16. When was the diagnosis of cluster headache made?

.....

17. Who made the diagnosis?

.....

18. How many doctors did you see before your cluster headache was diagnosed?

.....

19. Are you satisfied with your current treatment?

Yes **No**

20. Do you feel your GP is knowledgeable about your condition?

Yes **No**

21. Do you feel your GP appreciates how painful your cluster headache can be?

Yes **No**

22. Do you think the Organisation for the Understanding of Cluster Headache (OUCH) provided adequate information about cluster headache?

Yes **No**

23. Do you think the Organisation for the Understanding of Cluster Headache (OUCH) provided adequate support for you?

Yes **No**

24. On a scale of 1-10, in general how much has the cluster headache changed your life? 1 being the least and 10 being the most.

Little 1 2 3 4 5 6 7 8 9 10 a lot

25. On a scale of 1-10, what areas in your life have been mostly affected?

Social (such as friends) 1 2 3 4 5 6 7 8 9 10 a lot

Professional (such as work) 1 2 3 4 5 6 7 8 9 10 a lot

Private (such as family) 1 2 3 4 5 6 7 8 9 10 a lot

CLUSTER HEADACHE QUALITY OF LIFE QUESTIONNAIRE.

How many times have you experienced a Cluster Headache attack during the last month?_____

Please complete the following items to indicate how often Cluster Headache has affected various aspects of your life DURING THE LAST MONTH or DURING YOUR MOST RECENT CLUSTER HEADACHE EPISODE

Please tick only one box for each item. Do not leave any item blank.

Due to Cluster Headache, in the past month or last episode, how often have you:	**Never**	**Occasionally**	**Sometimes**	**Often**	**Always**
1. Avoided making plans due to unpredictability of Cluster Headache (eg Holidays)?					
2. Generally enjoyed the things that you do?					
3. Felt that the severity of Cluster Headache affected your daily activities?					
4. Felt negative or pessimistic about the future?					
5. Avoided leaving the house?					
6. Had to give up something that you enjoyed like alcohol or smoking?					
7. Felt frustrated?					
8. Avoided crowded and noisy places, e.g. public transport, pubs etc?					
9. Felt less interested in sexual relations?					
10. Felt unable to complete duties at work?					
11. Avoided potential headache triggers? e.g: alcohol, bright light, perfume, noise?					
12. Been unable to think clearly?					
13. Felt tense or anxious?					
14. Felt happy or satisfied with your personal life?					
15. Been less involved in family affairs, e.g: interaction with children, planning holidays?					
16. Been unable to take care of your appearance? (e.g: take a bath, put make-up on, change clothes etc?					
17. Felt isolated, lonely and vulnerable?					
18. Had problems with close personal relationships?					
19. Dreaded that the headache would not go away?					
20. Felt that others are dismissive of your Cluster Headaches?					
21. Been unable to socialize/ spend time with friends and family?					
22. Had problems concentrating, eg reading paper, watching TV etc?					

Due to Cluster Headache, in the past month or last episode, how often have you:	Never	Occasionally	Sometimes	Often	Always
23. Been forgetful, e.g: missed appointments?					
24. Felt like harming yourself or suicidal?					
25. Had to be alone during a Cluster Headache episode?					
26. Felt bad about yourself, lost self-confidence or felt worthless?					
27. Felt aggressive?					
28. Had difficulty in getting involved in leisure activities eg cinema, theatre, etc?					
29. Found your pain is unbearable if untreated?					
30. Been unable to achieve your daily goals and carry out routines and chores?					
31. Felt lacking in energy and constantly tired?					
32. Felt you were a burden on family and friends?					
33. Felt sleepy, worn out or less able to concentrate due to nocturnal attacks of Cluster Headache?					
34. Felt you had to revise your plans for the future?					
35. Felt that you were losing control over your health and over your own life?					
36. Felt self conscious and uncomfortable about your appearance after a Cluster Headache attack (e.g. swelling/redness of eyes and facial sweating etc)?					
37. Been restless, could not sit still, paced up and down?					
38. Felt less sensitive to (or more tolerant of) pain?					
39. Felt less respected by others?					
40. Experienced a general lack of motivation to do things?					
41. Been irritable, impatient or less tolerant?					
42. Felt stronger as a person as a result of coping with Cluster Headache?					
43. Had to rely on family or close friends for help?					
44. Contributed to household duties e.g., housework, cooking etc?					
45. Felt depressed, sad or tearful?					
46. Were unable to go to work (or stopped working)?					
47. Felt frightened or worried about getting a headache in public?					

Please rate your overall satisfaction with your life by placing a vertical line on the scale below at an appropriate point.

EUROQOL EQ-5D

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility

I have no problems walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-care

I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

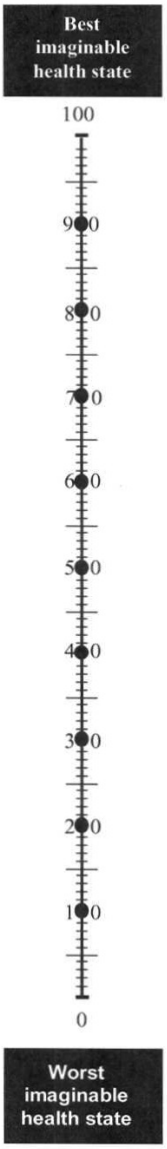
Anxiety/Depression

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today



SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Patient Name: _____

SSN#: _____ Date: _____

Person heling to complete this form: _____

1. In general, would you say your health is:

   - ❑ Excellent
   - ❑ Very good
   - ❑ Good
   - ❑ Fair
   - ❑ Poor

2. Compared to one year ago, how would you rate your health in general now?

   - ❑ Much better now than a year ago
   - ❑ Somewhat better now than a year ago
   - ❑ About the same as one year ago
   - ❑ Somewhat worse now than one year ago
   - ❑ Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

   a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

   b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

   c. Lifting or carrying groceries.
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

   d. Climbing several flights of stairs.
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

   e. Climbing one flight of stairs.
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

   f. Bending, kneeling or stooping.
      - ❑ Yes, limited a lot.
      - ❑ Yes, limited a little.
      - ❑ No, not limited at all.

g. Walking more than one mile.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

h. Walking several blocks.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

i. Walking one block.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

j. Bathing or dressing yourself.
- ❑ Yes, limited a lot.
- ❑ Yes, limited a little.
- ❑ No, not limited at all.

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?
☐ Yes ☐ No

b. Accomplished less than you would like?
☐ Yes ☐ No

c. Were limited in the kind of work or other activities
☐ Yes ☐ No

d. Had difficulty performing the work or other activities (for example, it took extra time)
☐ Yes ☐ No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?
☐ Yes ☐ No

b. Accomplished less than you would like
☐ Yes ☐ No

c. Didn't do work or other activities as carefully as usual
☐ Yes ☐ No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
- ❑ Not at all
- ❑ Slightly
- ❑ Moderately
- ❑ Quite a bit
- ❑ Extremely

7. How much bodily pain have you had during the past 4 weeks?
- ❑ Not at all
- ❑ Slightly
- ❑ Moderately
- ❑ Quite a bit
- ❑ Extremely

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- ❑ Not at all
- ❑ Slightly
- ❑ Moderately
- ❑ Quite a bit
- ❑ Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

a. did you feel full of pep?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

b. have you been a very nervous person?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

c. have you felt so down in the dumps nothing could cheer you up?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

d. have you felt calm and peaceful?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

e. did you have a lot of energy?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

f. have you felt downhearted and blue?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

g. did you feel worn out?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

h. have you been a happy person?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

i. did you feel tired?
- ❑ All of the time
- ❑ Most of the time
- ❑ A good bit of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?
- ❑ All of the time
- ❑ Most of the time
- ❑ Some of the time
- ❑ A little of the time
- ❑ None of the time

11. How TRUE or FALSE is each of the following statements for you?

a. I seem to get sick a little easier than other people
- ❑ Definitely true
- ❑ Mostly true
- ❑ Don't know
- ❑ Mostly false
- ❑ Definitely false

b. I am as healthy as anybody I know
- ❑ Definitely true
- ❑ Mostly true
- ❑ Don't know
- ❑ Mostly false
- ❑ Definitely false

c. I expect my health to get worse
- ❑ Definitely true
- ❑ Mostly true
- ❑ Don't know
- ❑ Mostly false
- ❑ Definitely false

d. My health is excellent
- ❑ Definitely true
- ❑ Mostly true
- ❑ Don't know
- ❑ Mostly false
- ❑ Definitely false

Please indicate the extent to which your cluster headache has interfered with your daily life in the PAST MONTH, by circling the appropriate response for each item.

1 Has your cluster headache interfered with how well you dealt with family, friends and others	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
2 Has your cluster headache interfered with your leisure time activities such as reading or exercising	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
3 As a result of your cluster headache had difficulty in performing work or daily activities	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
4 Has your chuster headache kept you from getting as much done at work or at home	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
5 Has your cluster headache limited your ability to concentrate on work or daily activities	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
6 Has your cluster headache left you too tired to do work or daily activities	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
7 Has you cluster headache limited the number of days you felt energetic	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
8 As a result of your cluster headache canceled work or daily activities...	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
9 As a result of your cluster headache needed help in handling routine tasks	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
10 As a result of your cluster headache stopped work or daily activities ...	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
11 As a result of your cluster headache you have not been able to go to social activity	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
12 As a result of your cluster headache felt fed up or frustrated	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
13 As a result of your cluster headache felt like a burden on others	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
14 As a result of your cluster headache felt afraid of letting others down	*A little bit of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*

McGill Pain Questionnaire

Some of the words you will read below describe pain. Please read each small group and choose the word that best describes your experience of pain in the LAST MONTH, and underline it. Choose only one word in each group which applies most to your pain. If none of the words in a group apply to you, please leave them and continue with the next group of words.

1. Flickering, Quivering, Pulsing, Trobbing, Beating, Pounding
2. Jumping, Flashing, Shooting
3. Pricking, Boring, Drilling, Stabbing, Lancinating
4. Sharp, Cutting, Lacerating
5. Pinching, Pressing, Gnawing, Cramping, Crushing
6. Tugging, Pulling, Wrenching
7. Hot, Burning, Scalding, Searing
8. Tingling, Itchy, Smarting, Stinging
9. Dull, Sore, Hurting, Aching, Heavy
10. Tender, Taut, Rasping, Splitting
11. Tiring, Exhausting
12. Sickening, Suffocating
13. Fearful, Frightening, Terrifying
14. Punishing, Gruelling, Cruel, Vicious, Killing
15. Wretched, Blinding
16. Annoying, Troublesome, Miserable, Intense, Unbearable
17. Spreading, Radiating, Penetrating, Piercing
18. Tight, Numb, Drawing, Squeezing, Tearing
19. Cool, Cold, Freezing
20. Nagging, Nauseating, Agonising, Dreadful, Torturing

Acceptance of Illness

For each statement, please tick the box that best describes how you felt about your illness in the LAST MONTH.

	Strongly disagree	Mildly disagree	Neither agree or disagree	Mildly agree	Strongly agree
I have a hard time adjusting to my illness.	☐	☐	☐	☐	☐
My illness makes me feel useless at times.	☐	☐	☐	☐	☐
Because of my illness, I miss things I like to do the most.	☐	☐	☐	☐	☐
Health problems make me more dependent on others.	☐	☐	☐	☐	☐
People are often uncomfortable around me because of my illness.	☐	☐	☐	☐	☐
I will never be self-sufficient enough to make me happy.	☐	☐	☐	☐	☐
My illness makes me a burden on family and friends.	☐	☐	☐	☐	☐
My illness does NOT make me inadequate.	☐	☐	☐	☐	☐

Stigma Scale

The aim of the ratings is to find out how your illness affects your interactions with other people.

For each item, please circle the appropriate number to indicate the extent to which your illness has affected your interactions with other people in the LAST MONTH.

	Not Much	Not At all	Sometimes	Definitely
1) I avoid other people.	0	1	2	3
2) I feel that other people are avoiding me.	0	1	2	3
3) I feel less attractive than I used to.	0	1	2	3
4) I feel odd and different from other people.	0	1	2	3
5) I feel self-conscious.	0	1	2	3
6) When I meet new people, I explain my problem to them.	0	1	2	3

SELF-ESTEEM

Below are a number of statements which people sometimes make about themselves. Read each statement and tick the box which indicates how you agree or disagree with what it says.

	Strongly Agree	Agree	Disagree	Strongly disagree
1. On the whole I am satisfied with myself.	☐	☐	☐	☐
2. At times I think I am no good at all.	☐	☐	☐	☐
3. I feel that I have a number of good qualities.	☐	☐	☐	☐
4. I am able to do things as well as most other people.	☐	☐	☐	☐
5. I feel I do not have much to be proud of.	☐	☐	☐	☐
6. I certainly feel useless at times.	☐	☐	☐	☐
7. I feel that I am person of worth, at least on an equal plane with others.	☐	☐	☐	☐
8. I wish I could have more respect for myself.	☐	☐	☐	☐
9. All in all, I am inclined to feel that I am a failure.	☐	☐	☐	☐
10. I take a positive attitude toward myself.	☐	☐	☐	☐

SOCIAL SUPPORT

The following questions ask about people in your environment who provide you with help or support. Each question has two parts. For the first part, list all the people you know, excluding yourself, whom you can count on for help or support in the manner described. Give the person's initials and their relationship to you (see example). Do not list more than one person next to each of the numbers beneath the question.
For the second part, circle how satisfied you are with the overall support you have.

If you have no support for a question, check the words "No one" but still rate your level of satisfaction. Do not list more that nine persons per question.
Please answer all questions as best you can. All your responses will be kept confidential.

EXAMPLE
Who can you count on to listen openly and uncritically to your innermost feelings?

No one	**1) T. N. (brother)**	**4) T. N. (father)**	**7)**
	2) L. M.(friend)	**5) L. M. (employer)**	**8)**
	3) R. S. (friend)	**6)**	**9)**

How satisfied?

6-very satisfied	**5-fairly satisfied**	**4-a little satisfied**	**3-a little dissatisfied**	**2-fairly dissatisfied**	**1-very dissatisfied**

1. Who can you really count on to provide you with <u>practical support</u> (eg take care of children, do housework, help out financially in short term, etc) when you need it in a crisis situation or time of stress?

No one	1)	4)	7)
	2)	5)	8)
	3)	6)	9)

How satisfied?

6-very satisfied	5-fairly satisfied	4- a little satisfied	3- a little dissatisfied	2- fairly dissatisfied	1- very dissatisfied

2. Who can you really count on to provide you with <u>emotional and mental support</u> (eg listen to you, console you, give you feedback, hug you, etc) when you need it in a crisis situation or time of stress?

No one	1)	4)	7)
	2)	5)	8)
	3)	6)	9)

How satisfied?

6-very satisfied	5-fairly satisfied	4- a little satisfied	3- a little dissatisfied	2- fairly dissatisfied	1- very dissatisfied

MIDAS QUESTIONNAIRE

Name : _____ **Date:** _____

Date of Birth: _____ **Hospital Number:** _____

INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months		
1.	On how many days in the last 3 months did you miss work or school because of your headaches	|_|_| days
2.	How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches *(Do not include days you counted in question 1 where you missed work or school)* ?	|_|_| days
3.	On how many days in the last 3 months did you not do household work because of your headaches ?	|_|_| days
4.	How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches *(Do not include days you counted in question 3 where you did not do household work)* ?	|_|_| days
5.	On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches?	|_|_| days
A.	On how many days in the last 3 months did you have a headache ? (If a headache lasted more than one day, count each day)	|_|_| days
B.	On a scale of 0 - 10, on average how painful were these headaches ? *(where 0 = no pain at all, and 10 = pain as bad as it can be)*	|_|_|
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MIDAS score (Add the total number of days from questions 1-5; ignore A and B) 0-5 little disability; 6-10 mild disability; 11-20 moderate disability; 21+ severe disability.

HEADACHE IMPACT TEST (HIT-6)

Name..... Hospital Number..... Date...../...../.....

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1 **When you have headaches, how often is the pain severe?**

Never Rarely Sometimes Very Often Always

2 **How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?**

Never Rarely Sometimes Very Often Always

3 **When you have a headache, how often do you wish you could lie down?**

Never Rarely Sometimes Very Often Always

4 **In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?**

Never Rarely Sometimes Very Often Always

5 **In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?**

Never Rarely Sometimes Very Often Always

6 **In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?**

Never Rarely Sometimes Very Often Always

COLUMN 1	COLUMN 2	COLUMN 3	COLUMN 4	COLUMN 5
(6 points each)	(8 points each)	(10 points each)	(11 points each)	(13 points each)

To score, add points for answers in each column. Total Score ☐

Higher scores indicate greater impact on your life.

Score range is 36–78.

The Henry Ford Disability Inventory (HDI)

Name : _____ **Date:** _____

Date of Birth: _____ **Hospital Number:** _____

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing because of your headaches. Please answer "yes" "sometimes" or "no" to each item. Answer each item as it pertains to your headaches only.

Tick only one box in each section

1 Because of my headaches I feel handicapped:
4 Yes
2 Sometimes
0 No

2 Because of my headaches I feel restricted in performing my daily routines:
4 Yes
2 Sometimes
0 No

3 No one understands the effect that my headaches have on my life:
4 Yes
2 Sometimes
0 No

4 I restrict my recreational activities (e.g. sports hobbies) because of my headaches:
4 Yes
2 Sometimes
0 No

5 My headaches make me angry:
4 Yes
2 Sometimes
0 No

6 Sometimes I feel that I am going to lose control because of my headaches:
4 Yes
2 Sometimes
0 No

7 Because of my headaches I am less likely to socialize:
4 Yes
2 Sometimes
0 No

14 My headaches place stress on my relationship with family or friends:
4 Yes
2 Sometimes
0 No

15 I avoid being around people when I have a headache:
4 Yes
2 Sometimes
0 No

16 I believe my headaches are making it difficult for me to achieve my goals in life:
4 Yes
2 Sometimes
0 No

17 I am unable to think clearly because of my headaches:
4 Yes
2 Sometimes
0 No

18 I get tense (e.g. muscle tension) because of my headaches:
4 Yes
2 Sometimes
0 No

19 I do not enjoy social gatherings because of my headaches:
4 Yes
2 Sometimes
0 No

20 I feel irritable because of my headaches:
4 Yes
2 Sometimes
0 No

8 **My spouse (significant other) or family and friends have no idea what I am going through because of my headaches:**

4 Yes
2 Sometimes
0 No

9 **My headaches are so bad that I feel I am going to go insane:**

4 Yes
2 Sometimes
0 No

10 **My outlook on the world is affected by my headaches:**

4 Yes
2 Sometimes
0 No

11 **I am afraid to go outside when I feel that a headache is starting:**

4 Yes
2 Sometimes
0 No

12 **I feel desperate because of my headaches:**

4 Yes
2 Sometimes
0 No

13 **I am concerned that I am paying penalties at work or at home because of my headaches:**

4 Yes
2 Sometimes
0 No

21 **I avoid traveling because of my headaches:**

4 Yes
2 Sometimes
0 No

22 **My headaches make me feel confused:**

4 Yes
2 Sometimes
0 No

23 **My headaches make me feel frustrated:**

4 Yes
2 Sometimes
0 No

24 **I find it difficult to read because of my headaches:**

4 Yes
2 Sometimes
0 No

25 **I find it difficult to focus my attention away from my headaches and on other things:**

4 Yes
2 Sometimes
0 No

The Pain Behaviour Checklist

Below are a range of activities that people who experience pain engage in or avoid in trying to cope with the pain. In trying to cope with your pain, please indicate whether you have engaged in or avoided these activities in the LAST MONTH, by selecting "YES", "NO" or "NA" (not applicable) for each item.

1. Take a tablet prescribed by a doctor	YES	NO	NA
2. Avoid or minimize lifting heavy objects	YES	NO	NA
3. Avoid or minimise travelling by public transport	YES	NO	NA
4. Apply some form of heat (eg hot water bottle)	YES	NO	NA
5. Avoid or reduce cooking	YES	NO	NA
6. Tell someone in your immediate family about the pain	YES	NO	NA
7. Avoid or minimize going to restaurants	YES	NO	NA
8. Avoid or minimize walking up and down stairs	YES	NO	NA
9. Avoid or reduce gentle exercise	YES	NO	NA
10. Grip rub or stroke the site of pain	YES	NO	NA
11. Avoid or reduce heavy housework (eg vacuum cleaning)	YES	NO	NA
12. Avoid or reduce bright lights	YES	NO	NA
13. Sit on a hard backed chair	YES	NO	NA
14. Cry	YES	NO	NA
15. Avoid or reduce going to work	YES	NO	NA
16. Avoid or minimize bending	YES	NO	NA
17. Distract yourself by reading, TV, etc	YES	NO	NA
18. Avoid or minimize gardening	YES	NO	NA
19. Avoid walking for short distances	YES	NO	NA
20. Avoid too much standing or sitting	YES	NO	NA
21. Tell a close friend about the pain	YES	NO	NA
22. Avoid or reduce time spent on hobbies not requiring physical exertion	YES	NO	NA
23. Avoid or minimize cleaning the car	YES	NO	NA
24. Avoid or minimize shopping	YES	NO	NA
25. Limp or drag your legs	YES	NO	NA

26. Avoid or reduce going to the pub	YES	NO	NA
27. Avoid or reduce sexual intercourse	YES	NO	NA
28. Take a tablet not prescribed by a doctor	YES	NO	NA
29. Avoid or minimize going out to visit family or friends	YES	NO	NA
30. Sigh, moan or cry out	YES	NO	NA
31. Avoid or reduce travelling in cars	YES	NO	NA
32. Avoid or reduce going to parties	YES	NO	NA
33. Lie on floor or hard bed	YES	NO	NA
34. Avoid or reduce loud noise	YES	NO	NA
35. Go swimming or try other forms of exercise to relieve the pain	YES	NO	NA
36. Avoid or reduce going to the cinema or theatre	YES	NO	NA
37. Change your posture	YES	NO	NA
38. Avoid or minimize doing odd jobs around the house	YES	NO	NA
39. Avoid spending time with people you live with	YES	NO	NA
40. Have a strong alcoholic drink	YES	NO	NA
41. Have your back massaged	YES	NO	NA
42. Avoid or reduce light housework (eg dusting, washing up)	YES	NO	NA
43. Talk to an acquaintance about the pain	YES	NO	NA
44. Avoid or reduce going out to dances or discos	YES	NO	NA
45. Slow down in all your physical movements	YES	NO	NA
46. Avoid or minimize stretching	YES	NO	NA
47. Grimace, frown or pull a face	YES	NO	NA
48. Avoid or reduce having visitors round to see you	YES	NO	NA
49. Avoid or reduce carrying	YES	NO	NA
50. Pace up and own	YES	NO	NA
51. Curl up in bed with a pillow	YES	NO	NA
52. Avoid or minimize doing tasks requiring concentration	YES	NO	NA
53. Avoid or minimize driving	YES	NO	NA
54. Change your eating pattern/habits (eg eat less or more carbohydrates or sweets)	YES	NO	NA

Ways of Coping

Please think about the ways in which you have tried to deal with the problems and feelings which you have experienced as a result of having CLUSTER HEADACHE. For each strategy listed below, please indicate the extent to which you have used it to cope with your torticollis during the LAST MONTH. Then put a tick in the most appropriate box.

	Never	Rarely	Some -times	Often	All the time
1. Got help with day to day chores or travel	( )	( )	( )	( )	( )
2. Blamed myself	( )	( )	( )	( )	( )
3. Concentrated on something good that would come out of the whole thing	( )	( )	( )	( )	( )
4. Went along with fate, sometimes I just have bad luck	( )	( )	( )	( )	( )
5. Went on as if nothing had happened	( )	( )	( )	( )	( )
6. Tried to keep my feelings to myself	( )	( )	( )	( )	( )
7. Hoped a miracle would happen	( )	( )	( )	( )	( )
8. Criticized or took it out on myself	( )	( )	( )	( )	( )
9. Looked for the silver lining, so to speak, tried to look on the bright side of things	( )	( )	( )	( )	( )
10. Slept more than usual	( )	( )	( )	( )	( )
11. Accepted sympathy and under-standing from someone	( )	( )	( )	( )	( )
12. Tried to forget the whole thing	( )	( )	( )	( )	( )
13. Let my feelings out somehow	( )	( )	( )	( )	( )
14. Talked to someone other than a doctor who could do something concrete about the problem	( )	( )	( )	( )	( )
15. Got away from it for a while, tried to rest or take a vacation	( )	( )	( )	( )	( )

	Never	Rarely	Some -times	Often	All the time
16. Tried to make my-self feel better by eating, drinking or smoking	( )	( )	( )	( )	( )
17. Found new faith	( )	( )	( )	( )	( )
18. Maintained my pride and kept a stiff upper lip	( )	( )	( )	( )	( )
19. Rediscovered what is important in life	( )	( )	( )	( )	( )
20. Avoided being with people in general	( )	( )	( )	( )	( )
21. Didn't let it get to me; refused to think too much about it	( )	( )	( )	( )	( )
22. Asked someone I respected other than a doctor for advice	( )	( )	( )	( )	( )
23. Kept others from knowing how bad things were	( )	( )	( )	( )	( )
24. Made light of the situation; refused to get too serious about it	( )	( )	( )	( )	( )
25. Talked to someone about who I was feeling	( )	( )	( )	( )	( )
26. Tried to work out what the problems were and what made my illness better or worse, and used it as a plan of action	( )	( )	( )	( )	( )
27. Refused to accept that it had happened	( )	( )	( )	( )	( )
28. Accepted it, since nothing could be done	( )	( )	( )	( )	( )
29. Tried to keep my feelings and illness from interfering with other things too much	( )	( )	( )	( )	( )
30. Wished that I could change what happened	( )	( )	( )	( )	( )
31. Changed the way I did things so that illness was less of a problem	( )	( )	( )	( )	( )

	Never	Rarely	Some -times	Often	All the time
32. Wished that I would change the way I felt	( )	( )	( )	( )	( )
33. Wished that the situation would go away or somehow be over with	( )	( )	( )	( )	( )
34. Had fantasies or wishes about how things might turn out	( )	( )	( )	( )	( )
35. Prayed	( )	( )	( )	( )	( )
36. Prepared myself for the worst	( )	( )	( )	( )	( )
37. Reminded myself that things could be worse	( )	( )	( )	( )	( )
38. Daydreamed or imagined a better time or place than the one I was in	( )	( )	( )	( )	( )
39. Wished I was a stronger person	( )	( )	( )	( )	( )
40. Joked about it	( )	( )	( )	( )	( )
41. Felt like I changed or grew as a person in a good way	( )	( )	( )	( )	( )
42. Remembered when my life was more difficult	( )	( )	( )	( )	( )
43. Felt bad that I couldn't avoid the problem	( )	( )	( )	( )	( )
44. Looked up medical information	( )	( )	( )	( )	( )
45. Thought about fantastic or unreal things that made me feel better	( )	( )	( )	( )	( )
46. Saw the doctor and did what was recommended	( )	( )	( )	( )	( )
47. Came up with a couple of solutions to the problem	( )	( )	( )	( )	( )
48. Remember past successes in my life	( )	( )	( )	( )	( )

	Never	Rarely	Some -times	Often	All the time
49. Did something totally new that I never would have done if my illness hadn't happened	( )	( )	( )	( )	( )
50. Religion became more important to me	( )	( )	( )	( )	( )
51. Read books or articles about my illness	( )	( )	( )	( )	( )
52. Concentrated on following the doctor's orders	( )	( )	( )	( )	( )
53. Tried to work it out by myself	( )	( )	( )	( )	( )
54. Faced the situation head on	( )	( )	( )	( )	( )
55. Took it out on other people	( )	( )	( )	( )	( )
56. Turned to work or other activities to take mind off the problem	( )	( )	( )	( )	( )
57. Thought about people who were worse off than me	( )	( )	( )	( )	( )
58. Decided to make my physical appearance less important in my life	( )	( )	( )	( )	( )
59. Tried to contact other people who had experienced the same illness and problems	( )	( )	( )	( )	( )
60. Hoped that a cure or new treatment would become available	( )	( )	( )	( )	( )
61. Told myself I had other things in life to be thankful for	( )	( )	( )	( )	( )
62. Tried to see a number of specialists and tried a variety of treatments	( )	( )	( )	( )	( )

HAD SCALE

Name : _____ **Date:** _____

Date of Birth: _____ **Hospital Number:** _____

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than long thought-out responses

Tick only one box in each section

A I feel tense or "wound up":
3 Most of the time
2 A lot of the time
1 Time to time, occassionally
0 Not at all

D I feel as if I am slowed down:
3 Nearly all the time
2 Very often
1 Sometimes
0 Not at all

D I can laugh and see the funny side of things:
0 As much as I always could
1 Not quite so much now
2 Definitely not so much now
3 Not at all

A I get a sort of frightened feeling like "butterflies" in the stomach:
0 Not at all
1 Occassionally
2 Quite often
3 Very often

A I get a sort of frightened feeling as if something awful is about to happen:
3 Very definitely and quite badly
2 Yes, but not too bad
1 A little but it does not worry me
0 Not at all

D I have lost interest in my appearance:
3 Definitely
2 I don't take so much care as I should
1 I may not take quite as much care
0 I take just as much care as ever

D I still enjoy the things I used to enjoy:
0 Definitely as much
1 Not quite so much
2 Only a little
3 Hardly at all

A I feel restless as if I have to be on the move:
3 Very much indeed
2 Quite a lot
1 Not very much
0 Not at all

A Worrying thoughts go through my mind:
3 A great deal of time
2 A lot of time
1 From time to time but not so often
0 Only occassionally

D I look forward with enjoyment to things:
0 As much as I ever did
1 Rather less than I used to
2 Definitely less than as I used to
3 Hardly at all

D I feel cheerful:
3 Not at all
2 Not often
1 Sometimes
0 Most of the time

A I get sudden feelings of panic:
3 Very often indeed
2 Quite often
1 Not very often
0 Not at all

A I can sit at ease and feel relaxed
0 Definitely
1 Usually
2 Not often
3 Not at all

D I can enjoy a good book or TV programme:
0 Often
1 Sometimes
2 Not often
3 Very seldom

Name: Today's Date:

Please answer each question below by putting a mark in the box which best describes you.

1. Are you interested in learning new things?	Not at all	slightly	some	a lot
2. Does anything interest you?	Not at all	slightly	some	a lot
3. Are you concerned about your condition?	Not at all	slightly	some	a lot
4. Do you put much effort into things?	Not at all	slightly	some	a lot
5. Are you always looking for something to do?	Not at all	slightly	some	a lot
6. Do you have plans and goals for the future?	Not at all	slightly	some	a lot
7. Do you have motivation?	Not at all	slightly	some	a lot
8. Do you have the energy for daily activities?	Not at all	slightly	some	a lot
9. Does someone have to tell you what to do each day?	Not at all	slightly	some	a lot
10. Are you indifferent to things?	Not at all	slightly	some	a lot
11. Are you unconcerned with many things?	Not at all	slightly	some	a lot
12. Do you need a push to get started on things?	Not at all	slightly	some	a lot
13. Are you neither happy nor sad, just in between?	Not at all	slightly	some	a lot
14. Do you consider yourself apathetic?	Not at all	slightly	some	a lot

BHS®

Date:_____

Name:_____ Marital Status:_____ Age:_____ Sex:_____

Occupation:_____ Education:_____

This questionnaire consists of 20 statements. Please read the statements carefully one by one. If the statement describes your attitude for the **past week including today,** darken the circle with a 'T' indicating TRUE in the column next to the statement. If the statement does not describe your attitude, darken the circle with an 'F' indicating FALSE in the column next to this statement. **Please be sure to read each statement carefully.**

1.	I look forward to the future with hope and enthusiasm.	Ⓣ Ⓕ
2.	I might as well give up because there is nothing I can do about making things better for myself.	Ⓣ Ⓕ
3.	When things are going badly, I am helped by knowing that they cannot stay that way forever.	Ⓣ Ⓕ
4.	I can't imagine what my life would be like in ten years.	Ⓣ Ⓕ
5.	I have enough time to accomplish the things I want to do.	Ⓣ Ⓕ
6.	In the future, I expect to succeed in what concerns me most.	Ⓣ Ⓕ
7.	My future seems dark to me.	Ⓣ Ⓕ
8.	I happen to be particularly lucky, and I expect to get more of the good things in life than the average person.	Ⓣ Ⓕ
9.	I just can't get the breaks, and there's no reason I will in the future.	Ⓣ Ⓕ
10.	My past experiences have prepared me well for the future.	Ⓣ Ⓕ
11.	All I can see ahead of me is unpleasantness rather than pleasantness.	Ⓣ Ⓕ
12.	I don't expect to get what I really want.	Ⓣ Ⓕ
13.	When I look ahead to the future, I expect that I will be happier than I am now.	Ⓣ Ⓕ
14.	Things just won't work out the way I want them to.	Ⓣ Ⓕ
15.	I have great faith in the future.	Ⓣ Ⓕ
16.	I never get what I want, so it's foolish to want anything.	Ⓣ Ⓕ
17.	It's very unlikely that I will get any real satisfaction in the future.	Ⓣ Ⓕ
18.	The future seems vague and uncertain to me.	Ⓣ Ⓕ
19.	I can look forward to more good times than bad times.	Ⓣ Ⓕ
20.	There's no use in really trying to get anything I want because I probably won't get it.	Ⓣ Ⓕ

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24 A B C D E

GHQ28

Please read this carefully.

We should like to know if you have had any medical complaints and how your health has been in general, *over the past few weeks.* Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

Have you recently

AI	**been feeling perfectly well and in good health?**	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2	**been feeling in need of a good tonic?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A3	**been feeling run down and out of sorts?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A4	**felt that you are ill?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A5	**been getting any pains in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A6	**been getting a feeling of tightness or pressure in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
A7	**been having hot or cold spells?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B1	**lost much sleep over worry?**	Not atall	No more than usual	Rather more than usual	Much more than usual
B2	**had difficulty in staying asleep once you are off?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B3	**felt constantly under strain?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B4	**been getting edgy and bad-tempered?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B5	**been getting scared or panicky for no good reason?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B6	**found everything getting on top of you?**	Not at all	No more than usual	Rather more than usual	Much more than usual
B7	**been feeling nervous and strung-up all the time?**	Not at all	No more than usual	Rather more than usual	Much more than usual

Please turn over

Have you recently

C1	**been managing to keep yourself busy and occupied?**	More so than usual	Same asusual	Rather less than usual	Much less than usual
C2	**been taking longer over the things you do?**	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3	**felt on the whole you were doing things well?**	Better than usual	About the same	Less well than usual	Much less well
C4	**been satisfied with the way you've carried out your task?**	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
C5	**felt that you are playing a useful part in things?**	More so than usual	Same as usual	Less useful than usual	Much less useful
C6	**felt capable of making decisions about things?**	More so than usual	Same as usual	Less so thanusual	Much less capable
C7	**been able to enjoy your normal day-to-day activities?**	More so than usual	Same as usual	Less so than usual	Much less than usual

D1	**been thinking of yourself as a worthless person?**	Not at all	No more than usual	Rather more than usual	Much more than usual
D2	**felt that life is entirely hopeless?**	Not atall	No more than usual	Rather more than usual	Much more than usual
D3	**felt that life isn't worth living?**	Not at all	No more than usual	Rather more than usual	Much more than usual
D4	**thought of the possibility that you might make away with yourself?**	Definitely not	I don't thinkso	Has crossed my mind	Definitely have
D5	**found at times you couldn't do anything because your nerves were too bad?**	Not atall	No more than usual	Rather more than usual	Much more than usual
D6	**found yourself wishing you were dead and away from it all?**	Not at all	Nomore than usual	Rather more than usual	Much more than usual
D7	**found that the idea of taking your own life kept coming into your mind?**	Definitely not	I don't think so	Has crossed my mind	Definitely has

A	B	C	D	Total